SENSORY GATING AND SENSORIMOTOR GATING IN PSYCHIATRIC DISORDERS SHARING ATTENTION DEFICITS

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Dominique H. Holstein

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Prof. Dr. rer. nat. Lutz Jäncke and Prof. Dr. med. Franz Vollenweider

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ABSTRACT

Functional gating is an important function of the brain, preventing it from a sensory overload by filtering out irrelevant stimuli. A deficit in gating is characterized by a general reduction of the ability to gate sensory information. Moreover, a deficit in gating is characterized by a general reduction of the ability to gate intrusive sensory, motor and/or cognitive information. Two widely studied physiological parameters designed to assess central inhibition used in laboratory studies, are prepulse inhibition (PPI) of the acoustic startle response, considered as a form of sensorimotor gating, and suppression of the P50 auditory event-related potential (AEP) in a condition-test paradigm (P50 suppression), considered as a form of sensory gating.

While sensory gating and sensorimotor gating have been proposed to be endophenotypic biomarkers for schizophrenia spectrum disorders, deficient gating is not exclusively attributable to schizophrenia. Therefore, psychophysiological alterations like impaired gating have been reported in patients with posttraumatic stress disorder (PTSD), but the findings are still inconsistent, and potential relationships to symptomatology remain unclear. Moreover, even though there is an impaired perceptual capacity in attention-deficit/hyperactivity disorder (ADHD) patients, psychophysiological alterations, such as impaired PPI and P50 suppression, have not been reported in patients suffering from ADHD. Furthermore, there is considerable evidence that schizophrenia patients treated with atypical antipsychotics exhibit relatively less gating deficits than do other patients with schizophrenia. Therefore, recent studies have investigated the effect of antipsychotic medications on gating measures in healthy volunteers exhibiting low levels of gating, rather than in patients.

In the present thesis we investigated whether PTSD and ADHD patients exhibit deficits in sensory gating and/or sensorimotor gating compared to healthy control subjects. Furthermore, we investigated the influence of the antipsychotic sertindole vs. placebo in two separate experimental sessions, on both gating measures in male volunteers stratified for low and high baseline gating levels.

We showed that PTSD patients as well as ADHD patients showed impaired sensory gating but not sensorimotor gating. Moreover, sertindole increased PPI and P50 suppression in healthy volunteers exhibiting low baseline PPI and low baseline P50 suppression respectively, while sertindole attenuated gating in subjects exhibiting high baseline gating. Furthermore, subjects exhibiting low PPI chose worse strategy in a spatial working memory task.

We conclude that deficient P50 gating, neither related to specific psychopathological symptoms nor to specific impairment of cognitive performance, is a robust finding in PTSD

and adult ADHD. Consequently, P50 gating is not exclusively associated with a specific disorder. Furthermore, impaired P50 suppression might be a general and common feature of several psychiatric disorders sharing deficits in attention functions. However, the absence of diminished PPI in PTSD patients and adult ADHD patients seems to be a robust finding. Moreover, the influence of antipsychotics on sensory and sensorimotor gating in healthy volunteers seems to be dependent on baseline gating levels. Therefore, mixed D_2 / 5-HT_2 receptor antagonists modulate PPI as well as P50 suppression in a way to enhance it in healthy subjects with low baseline gating in a way comparable as seen in studies with schizophrenia patients. Thus, sensorimotor and sensory gating measures can be used as informative and independent neurophysiological markers for studies investigating neuropsychiatric disorders and may well constitute separable endophenotypes. While the combined use of PPI and P50 suppression in a single study might represent excellent tools for translational research, it still remains fundamental to assess established parameters for patients' studies as well as studies with healthy volunteers comparable to those coming from schizophrenia research to achieve constant and comparable and study overlapping data.

ZUSAMMENFASSUNG

Eine intakte sensorische Reizfilterleistung, welche für die Ausfilterung irrelevanter Stimuli zuständig ist, schützt das Gehirn vor einer sensorischen Reizüberflutung. Ein Filterleistungsdefizit ist durch eine generelle Reduktion der Fähigkeit, auf das Gehirn eindringende sensorische, motorische oder kognitive Informationen zu filtern, charakterisiert. Zwei in der Forschung häufig verwendete Parameter, welche als Mass für die zentrale Reizfilterleistung des Gehirns gelten, sind die so genannte Präpuls-Inhibition der akustischen Schreckreaktion (PPI) als Mass für die sensomotorische Reizfilterleistung, sowie die durch ein auditorisch evoziertes Potential entstehende P50 Suppressionsleistung, welche als Mass für sie sensorische Reizfilterleistung gilt. Beide Masse wurden als endophänotypische biologische Marker für Erkrankungen aus dem schizophrenen Formenkreis vorgeschlagen; Auffälligkeiten in beiden Massen treten aber nicht nur ausschliesslich im Bereich schizophrener Erkrankungen auf. So wurde eine verminderte Reizfilterleistung auch bei Patienten mit einer posttraumatischen Belastungsstörung (PTBS) gefunden, jedoch sind die Befunde hierzu inkonsistent. Hingegen wurden bei Patienten mit einer Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung (ADHS) keine sensomotorischen und sensorischen Reizfilterleistungsdefizite berichtet, obwohl diese Patientengruppe als Kernmerkmal an einer Beeinträchtigung der Aufmerksamkeit leidet und somit eine Beeinträchtigung der kortikalen Reizfilterleistung in Betracht gezogen werden muss. Zudem gibt es Hinweise, dass Patienten, welche an einer Schizophrenie leiden und mit einer atypischen neuroleptischen Medikation behandelt werden, weniger starke Beeinträchtigungen in ihrer Reizfilterleistung zeigen. Kürzlich haben Studien in gesunden Probanden mit einer tiefen sensorischen und sensomotorischen Reizfilterleistung systematisch die Wirkung einer neuroleptischen Medikation auf beide Masse untersucht.

In der vorliegenden Dissertation wurde untersucht, ob Patienten mit einer PTBS und Patienten mit einer ADHS im Vergleich zu gesunden Kontrollprobanden eine verminderte sensomotorische und/oder sensorische Reizfilterleistung aufweisen. Zusätzlich wurde der Einfluss des atypischen Neuroleptikums Sertindol im Vergleich zu Placebo auf die beiden Filtermasse in gesunden Probanden untersucht.

Es konnte gezeigt werden, dass sowohl Patienten mit einer PTBS, als auch Patienten mit einer ADHS eine verminderte sensorische Reizfilterleistung aufweisen. Hingegen unterschied sich die sensomotorische Reizfilterleistung in beiden Patientengruppen nicht von der Reizfilterleistung der gesunden Kontrollprobanden. Weiter konnte gezeigt werden, dass

Sertindol die Filterleistung in beiden Massen in gesunden Kontrollprobanden mit einer tiefen Baseline erhöhte, während es die Filterleistung von Kontrollprobanden mit einer hohen Baseline verminderte. Probanden mit einer tiefen sensomotorischen Baseline wählten zusätzlich eine schlechtere Strategie in einer Aufgabe zum räumlichen Arbeitsgedächtnis.

Die Ergebnisse der Studien weisen darauf hin, dass Patienten mit einer PTBS und Patienten mit einer ADHS eine verminderte sensorische Reizfilterleistung aufweisen, welche nicht an spezifische psychopathologische Symptome oder die Leistung in kognitiven Aufgaben gekoppelt ist. Eine verminderte P50 Suppressionsleistung ist somit nicht an ein spezifisches psychiatrisches Störungsbild gekoppelt, sondern könnte möglicherweise bei verschiedenen Störungsbildern auftreten, welche als Gemeinsamkeit eine Störung der Aufmerksamkeit aufweisen. Der Einfluss einer neuroleptischen Medikation auf die beiden Reizfiltermasse in gesunden Probanden scheint von deren Baseline abhängig zu sein. Es zeigt sich, dass gemischte D_2-/5-HT_2-Rezeptorantagonisten bei gesunden Probanden mit einer tiefen sensomotorischen als auch sensorischen Baseline zu einer Erhöhung der Reizfilterleistung führen. Diese ist mit den beschriebenen Verbesserungen in Patienten, welche unter einer Schizophrenie leiden und neuroleptisch behandelt werden, vergleichbar. Beide Paradigmen, PPI als auch die P50 Suppression, eignen sich somit als informative und unabhängige neurophysiologische Marker in der Untersuchung von neuropsychiatrischen Störungsbildern und könnten zu einer Endophänotypisierung beitragen. Obwohl sich der kombinierte Einsatz beider Filterleistungsmasse in einer Studie zur translationalen Forschung gut eignet, ist gleichzeitig auf die Einhaltung und Entwicklung von exakten Parametern beider Reizfiltermasse zu achten. Nur so können eine Konstanz der erhobenen Daten vorausgesetzt und die Ergebnisse aus den verschiedenen Studien miteinander verglichen werden. In erster Linie sollten hierfür die Empfehlungen zur Parameterbestimmung aus der Forschung zur Schizophrenie berücksichtig werden.

1. INTRODUCTION

1.1. Gating functions – inhibitory processes and time-linked information processing

A fundamental feature of information processing is the ability to inhibit, filter out, or gate extraneous stimuli and to attend to salient features of the environment. Functional gating is an important characteristic of the brain. This process prevents sensory overload of higher brain functions by filtering out irrelevant stimuli. A deficit in gating is characterized by a general reduction of the ability to gate intrusive sensory, motor and/or cognitive information (Braff & Geyer, 1990; Geyer et al., 1987). While theories first focused on the concept that information is processed through a sequence of 'steps' or 'stages' in a framework of sequential processing of informational stimuli, thought to occur at progressively "higher" sites in the central nervous system (Braff, Geyer, & Swerdlow, 2001), these models were challenged by a new generation of alternative 'integrationist' models, relying on neural network theory, which emphasizes that cascades of neurons in multiple loci create an integrated 'symphonic array' of time-coordinated events across multiple sites (Braff, Swerdlow, & Geyer, 1999; Braff et al., 2001). An impairment of information processing is thought to be found in several psychiatric disorders (Andreasen, 1999; Braff et al., 2001; Kirkpatrick et al., 2000; Swerdlow & Koob, 1987). Furthermore, since the mid-1970s there were an increasing number of cross-species translational studies of gating functions (Braff et al., 2001).

Two widely studied physiological parameters designed to assess central inhibition used in laboratory studies, are prepulse inhibition (PPI) of the acoustic startle response, considered as a form of sensorimotor gating, and suppression of the P50 auditory event-related potential (AEP) in a condition-test paradigm (P50 suppression), considered as a form of sensory gating.

1.1.1. Startle and prepulse inhibition (PPI) – measured by electromyography (EMG)

The startle reflex is a phylogenetic old motor reaction to an intense aversive sensory stimulus (visual, auditory or tactile) reflecting a protective automatic and irrepressible defensive mechanism (Turpin, 1986). It consists of a contraction of the skeletal and facial muscles in response to a sudden, intense stimulus, presentable across multiple modalities and can be studied across species, lending itself to translational research possibilities (Braff & Geyer, 1990; Geyer et al., 1987; Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001). In humans, startle reflex is typically measured by electromyography (EMG) of the orbicularis oculi muscle

(Graham, 1975). One form of its plasticity (others are habituation and fear potentiation) is the so called prepulse inhibition (PPI). PPI refers to the attenuation of the reflexive startle reaction elicited by an intense pulse stimulus when its presentation is preceded shortly (30 to 300 ms) by a weak prepulse stimulus (Graham, 1975; Hoffman & Ison, 1980). According to the 'protection of processing' theory formulated by Graham (Graham, 1975; Graham, 1980; Graham, 1992), the inhibitory effect of the prepulse upon subsequent pulse processing reflects the protection of the on-going processing of the antecedent prepulse against interference by the succeeding pulse. In practice, mostly a sudden loud burst of noise is used for pulse stimuli, and the magnitude of PPI is measured by the diminution of the startle response to the pulse stimulus due to the antecedent prepulse stimulus. For calculation most commonly PPI is indexed as percent of the startle amplitude (%PPI) in trials containing a prepulse (prepulse-pulse trials) relative to those trails containing only a pulse (pulse alone trails) stimulus. Furthermore, PPI occurs in all mammals, it occurs when the startling and prepulse stimuli are in the same or different sensory modalities, it is stable over time, and it is not a form of conditioning, because it occurs on the first exposure to prepulse and pulse-alone stimulation (Blumenthal, 1988; Blumenthal, Schicatano, Chapman, Norris, & Ergenzinger, Jr., 1996; Graham, 1980; Hoffman & Ison, 1980; Braff et al., 2001; Cadenhead, Carasso, Swerdlow, Geyer, & Braff, 1999). Activation of behavioral gating processes (e.g. PPI) is regulated by forebrain neural circuitry. Connections between limbic cortico-striato-pallido-pontine (CSPP) and related cortico-striato-pallido-thalamic (CSPT) circuitry, and the primary startle circuitry within the pons seem to regulate these inhibitory influences (Braff et al., 2001; Lee, Lopez, Meloni, & Davis, 1996; Swerdlow & Koob, 1987; Swerdlow, Caine, Braff, & Geyer, 1992). Moreover, while the forebrain neural circuitry exert a regulatory influence, the signal of the prepulse need not to traverse the CSPP circuitry (i.e. mediate via the forebrain circuitry) in order to produce PPI (Davis & Gendelmann, 1977).

1.1.2. P50 suppression – measured by electroencephalography (EEG)

The auditory sensory gating P50 suppression paradigm involves a condition-test paired-stimulation, in which a middle latency AEP, the so called P50 component, is measured by means of electroencephalography (EEG) (Adler, Freedman, Ross, Olincy, & Waldo, 1999). Comparably to PPI, in the P50 suppression paradigm two identically auditory stimuli are presented in succession at an interstimulus interval of approximately 500 ms. The first stimulus (conditioning stimulus) not only produces an AEP approximately 50 ms after stimulation (P50

wave) and is thought to activate excitatory pathways, and thus reflects the capacity of the neuronal system under study to respond, but also activates gating processes, resulting in a decrement of the P50 AEP to the second stimulus (test stimulus), which is thought to activate prevailingly inhibitory pathways (Adler et al., 2004; Csomor et al., 2008a). The reduction of the second stimulus reflects the strength of the inhibitory mechanisms activated by the first stimulus (Adler et al., 2004). Basically, P50 suppression is indexed as the ratio of test stimulus (S_2) to conditioning stimulus (S_1) amplitude (%P50). Failure to exhibit P50 suppression is often interpreted as evidence of a loss of normal inhibition (Freedman et al., 1987). P50 AEP has a component with a positive fronto-central topographic distribution and its generators are represented in both temporal lobes, including left and right superior temporal gyri (STG) and within the primary auditory cortex (PAC). The PAC is mainly in discussion to produce the auditory P50 component (Lee et al., 1984; Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994). Moreover, the P50 generation circuitry, especially in mesial temporal lobe structures has interacting and overlapping neural substrates with the CSPT circuitry involved in PPI (Leonard et al., 2002; Swerdlow & Koob, 1987; Swerdlow, Geyer, & Braff, 2001a).

Even though one might assume, that PPI and P50 suppression are conceptually comparable measuring both gating processes, there is empirical evidence that both measures are not associated, because they neither are correlated in human volunteers (Braff, Light, & Swerdlow, 2007; Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004; Light & Braff, 2001; Oranje, Geyer, Bocker, Leon, & Verbaten, 2006; Schwarzkopf, Lamberti, & Smith, 1993) nor in rodents (de Bruin, Ellenbroek, Cools, Coenen, & van Luijtelaar, 1999; Ellenbroek, van Frenken, & Cools, 1999; Swerdlow et al., 2006a). Furthermore, both gating mechanisms are differential sensitive to drug treatment (de Bruin et al., 1999; Ellenbroek et al., 1999; Csomor et al., 2008a). These findings suggest that different neuronal mechanisms are involved in the regulation of sensory gating and sensorimotor gating. Moreover, this understanding suggests the independent as well as conjoint use of sensory gating and sensorimotor gating measures for selection as biomarkers (Braff & Light, 2005; Braff et al., 2007). Therefore, in the last years sensory gating and sensorimotor gating measures are common used as physiological markers in psychiatric research to describe endophenotypes, especially in schizophrenia research (Geyer, 2006b).

1.2. Impaired sensory gating and/or sensorimotor gating in psychiatric disorders

It has been considered that deficits in early information processing (e.g. impaired sensory gating and/or sensorimotor gating) might be a central feature of several psychiatric disorders and are potentially leading to a sensory overload, conducting to cognitive deficits and general impairments (Braff et al., 2001; Csomor et al., 2008a). The most prominent domain of gating research has been established in schizophrenia spectrum disorders. In regard to the pathophysiology of the miscellaneous cognitive deficits observed in schizophrenia there is increasing evidence that schizophrenia patients exhibit functional deficits in different domains of early information processing (Braff et al., 2001; Light & Braff, 1999). Gating deficits may cause schizophrenic patients to become overloaded with excessive exteroceptive and interoceptive stimuli and leading to a state of 'flooding' (Venables, 1964) which in turn could direct to a breakdown of cognitive integrity (Brebion, Smith, Gorman, & Amador, 1996; Karper et al., 1996; McGhie & Chapman, 1961). Furthermore, this failure of inhibition has been stated to be correlated with psychopathological symptoms typically found in schizophrenia, so called 'positive symptoms' as perceptual disturbances (illusions or hallucinations) and delusions, and cognitive impairments (e.g. attention deficits, memory deficits, distractibility) (Braff & Geyer, 1990; Braff et al., 2001). Moreover, there has been successful attempts to find a relation between positive symptoms and impaired cognitive performance in patients suffering from schizophrenia (Braff et al., 1999; Ludewig, Geyer, & Vollenweider, 2003; Perry & Braff, 1994; Perry, Geyer, & Braff, 1999; Vollenweider, Benz, Hell, & Ludewig, 2004; Weike, Bauer, & Hamm, 2000). While patients with schizophrenia exhibit deficits in both, PPI (Braff et al., 1978; Braff et al., 2001) and P50 suppression (Adler et al., 1982; Baker et al., 1987; Cadenhead, 2002; Light & Braff, 1999; Takahashi et al., 2008), both measures seemed not to be correlated in patients as well as in healthy volunteers (Braff et al., 2007; Brenner et al., 2004; Light & Braff, 2001; Oranje et al., 2006; Schwarzkopf et al., 1993). Notwithstanding, both gating measures were impaired in the same cohort of patients suffering from schizophrenia (Braff et al., 2007). While, sensory gating and sensorimotor gating have been proposed to be endophenotypic biomarkers for schizophrenia spectrum disorders (Adler et al., 1982; Adler et al., 2004; Baker et al., 1987; Braff & Light, 2005; Cadenhead, 2002; Cadenhead, Light, Geyer, McDowell, & Braff, 2002; Geyer, 2006b; Gottesman & Gould, 2003; Light & Braff, 1999), deficient gating is not exclusively attributable to schizophrenia. Moreover, the findings coming from schizophrenia research suggest the independent as well as conjoint use of both gating measures for selection as

biomarkers in other psychiatric disorders (Braff & Light, 2005; Braff et al., 2007). Therefore, impaired PPI and/or P50 suppression have been reported in several other disorders as psychotic mania (Perry, Minassian, Feifel, & Braff, 2001), obsessive compulsive disorder (Hoenig, Hochrein, Quednow, Maier, & Wagner, 2005; Swerdlow, Benbow, Zisook, Geyer, & Braff, 1993), Huntington's disease (Swerdlow et al., 1995; Swerdlow et al., 2001b; Valls-Sole, Munoz, & Valldeoriola, 2004), Tourette's syndrome (Castellanos et al., 1996; Swerdlow, Zinner, Hartston, Filion, & Magulac, 1994b; Swerdlow, Zinner, Hartston, Filion, & Magulac, 1994a), autism (Perry, Minassian, Lopez, Maron, & Lincoln, 2007). In contrast to these findings, it is not yet established whether gating functions, as measured by means of PPI and P50 suppression, are impaired in patients suffering from posttraumatic stress disorder (PTSD) and patients with attention-deficit/hyperactivity disorder (ADHD), both sharing comparable attention deficits as the above mentioned disorders. The few studies investigating sensory gating and sensorimotor gating functions in ADHD patients revealed no differences between patients and healthy controls (Feifel, Minassian, & Perry, 2009; Hanlon, Karayanidis, & Schall, 2008; Olincy et al., 2000). Furthermore, most (Ghisolfi et al., 2004; Gillette et al., 1997; Neylan et al., 1999; Skinner et al., 1999) but not all (Metzger et al., 2002) studies revealed deficient P50 suppression in PTSD patients, but the findings in regard to PPI are rather inconsistent (Butler et al., 1990; Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon, Morgan Ill, Davis, & Southwick, 1998a; Grillon, Morgan, Davis, & Southwick, 1998b; Lipschitz et al., 2005; Ornitz & Pynoos, 1989). Consequently, the issue of whether sensory gating and/or sensorimotor gating are impaired in ADHD and PTSD remains rather inconsistent. Moreover, PPI and P50 suppression have not been assessed within the same patients' cohort of one of the two disorders, so that the inter-relationship among PPI and P50 suppression has never been assessed in the same subjects under investigation. Therefore, this thesis conducts in chapter 2 a study investigating both forms of gating functions and psychopathological symptoms in PTSD patients and in chapter 3 a study investigating both forms of gating functions and psychopathological symptoms in ADHD patients.

1.2.1. Methodological aspects

Even though the technical equipment to investigate PPI is 'easy-to-use' and widespread in laboratories all over the world, it is imperative to use an elaborated neurophysiological recording, an established parameter setting and data analysis. Besides a potential

pharmacological influence discussed later, the experimental parameter setting has an influence on sensory gating as well as on sensorimotor gating in humans and rodents. Therefore, the experimental setting plays an important planning factor in designing and planning a study (Braff et al., 2001). PPI stimuli typically are presented out of a continuous background noise so that one aspect of salience of prepulse is a reflection of the difference between background noise level an prepulse noise level (Braff et al., 2001). Stronger prepulses induce generally higher levels of PPI (Blumenthal, 1995; Csomor et al., 2006; Graham & Murray, 1977), and only prepulses from 6 to 18 dB_A above background noise produces stable PPI (Csomor, Vollenweider, Feldon, & Yee, 2005). In addition, there is evidence that white noise prepulse stimuli elicit maximal levels of PPI (Braff et al., 2001; Schell, Wynn, Dawson, Sinaii, & Niebala, 2000). Furthermore, stimulus onset asynchrony (SOA) are normally ranging from between 30 to 240 ms, as intervals of 1000 ms or more can elicit facilitation of the startle reflex (Braff et al., 1978; Braff et al., 2001; Graham, 1975; Graham, Putnam, & Leavitt, 1975; Harbin & Berg, 1986; Hoffman & Wible, 1969;). Variable inter-trial intervals (ITIs) have a range between 8 to 30 s, promoting less startle habituation compared to fix ITIs (Braff et al., 2001). Moreover, gender plays an important role as adult males have more robust PPI compared to female adults (Braff et al., 2001; Swerdlow et al., 1993), whose menstrual cycle is known to affect PPI. Therefore, sensorimotor gating is lower in luteal phase compared to the follicular (Jovanovic et al., 2004; Bannbers, Kask, Wikstrom, & Sundstrom, I, 2009). Although a part of the literature is based on the assumption that PPI is independent of the baseline startle reaction, there is accumulating evidence that argues against such an independency (Csomor et al., 2006; Csomor et al., 2008b; Sandner & Canal, 2007; Yee, Chang, Pietropaolo, & Feldon, 2005), revealing a monotonic dependency of PPI on the intensity of startle eliciting stimulus. Therefore, it is quiet important to observe baseline startle reactivity levels for a valuable interpretation of PPI as weaker startle reactions are accompanied by a higher PPI (Csomor et al., 2008b). Nevertheless, it has been discussed that variation in baseline startle reactivity in groups of comparison cannot be fully responsible for significant PPI differences between the same groups (Abel, Allin, Hemsley, & Geyer, 2003; Cilia, Hatcher, Reavill, & Jones, 2005).

In contrast to PPI less characterization of the experimental parameters has been established for P50 suppression research. Considerable variability in stimulus intensity and stimulus duration exists across the P50 suppression literature. More specifically, psychological stress and heightened facial muscle activation were found to modulate the P50 suppression ratio (Yee & White, 2001). Moreover, AEP P50 component has small amplitude and often its detection and quantification is difficult. Furthermore, when the intensity of the stimulus is too low, a distinct

P50 component is hardly evoked. Moreover, not only physical properties of the eliciting stimuli influence P50 suppression, but also psychological state factors, such as declines in attention or vigilance, fatigue, and drowsiness might have a influence (White & Yee, 2006). Furthermore, de Wilde, Bour, Dingemans, Koelman, and Linszen (2007) reported differences in P50 suppression according to the subject's position (upright vs. supine) during electrophysiological recording and concluded that the optimal level of sound intensity to elicit stable AEPs seems to be between 85 and 90 dB_A. Moreover, not all studies reported to have evaluated for hearing difficulties in their subjects.

Therefore, the use of a divergent parameter setting in different studies might have at least partly accounted for the conflicting findings in relation to sensory gating and/or sensorimotor gating, potentially complicating the direct comparison of results between studies dealing with gating. To this end, it is imperative to establish firm experimental parameters in sensory gating and sensorimotor gating research enabling effective comparisons of results between different laboratories. For all of our conducted studies reported later in this thesis, we used a parameter setting for PPI and P50 suppression paradigms well established in schizophrenia research.

1.2.2. Sensory gating and sensorimotor gating in patients suffering from posttraumatic stress disorder (PTSD)

Exposure to an intensely distressing traumatic event can trigger long-lasting behavioural changes conducting to the development of PTSD. PTSD disorder is characterized by a constellation of symptoms reflecting a prolonged adverse response. Three major symptoms are described as being characteristically for PTSD. There are intrusion and flashbacks to the traumatic event and avoidance of stimuli associated with the trauma on a mental and behavioural level. Furthermore, patients experience alterations in autonomic nervous system functions, such as physiological responses to trauma cues, a change of the basal tone resulting in a general hyperarousal, an exaggerated startle reaction, hypervigilance and insomnia (Yehuda, 2004). Moreover, patients suffering from PTSD also exhibit a deranged perceptual modulation and show more distractibility (Stewart & White, 2008).

The diagnosis of PTSD, like most other psychiatric diagnoses, is based on the verbal report of an individual comprising the severity and number of symptoms. The validity of diagnosis is greatly influenced by accuracy of the patient's self-reports and the clinician's ability to interpret the reported symptoms and to determine whether the diagnostic criteria are met.

Furthermore, the self-report of physiological disturbance is relied exclusively for evidence of somatic symptoms. In consideration of these facts Orr and Roth (2000) suggested to incorporate neurophysiological assessment as an additional source of information regarding whether certain PTSD symptoms are present or not. Moreover, such measures are less dependent on self-reports. Contrary to the suggestion of Orr et al. (2000) in clinical practice neither initial diagnostics nor follow-up examinations employ psychophysiological measures in spite of the fact that exaggerated startle response reflects one of the DSM-IV criteria for the diagnosis of PTSD (American Psychiatric Association, 2000). Nevertheless, during the past decade, there has been a growing interest in neurophysiological research in PTSD patients. Clinical observations supporting an association between exposure to life-threatening events and altered physiologic arousal have made trauma-related disorders obvious targets for neurophysiological assessment (Metzger et al., 2002; Orr, Metzger, & Pitman, 2002). Altered neurophysiological responses in patients suffering from PTSD have been found in a variety of neurophysiological measures like an increase of the startle reflex, diminished sensory gating and sensorimotor gating. However, the literature to date is inconclusive. Therefore, the applicability of neurophysiological assessment in order to support PTSD diagnosis remains questionable.

Inconsistent results have been found regarding deficient PPI in PTSD patients. Although, impaired PPI has been reported in children with PTSD (Ornitz & Pynoos, 1989) and Vietnam veterans with PTSD (Grillon et al., 1996; Grillon et al., 1998a), other studies could not replicate the findings of deficient PPI in patients suffering from PTSD (Butler et al., 1990; Grillon et al., 1998b; Lipschitz et al., 2005).

Analogously to the conflicting results of startle modulation (i.e. PPI) also studies investigating startle reactivity in PTSD patients report conflicting results in spite of the fact that exaggerated startle reflects a diagnostic criterion for the assessment of PTSD (DSM-IV criterion 5D). Increased startle reactivity indicating a state of hyperarousal has been reported in patients suffering from PTSD (Butler et al., 1990; Grillon et al., 1998b; Morgan Ill, Grillon, Southwick, Davis, & Charney, 1995; Orr, Lasko, Shalev, & Pitman, 1995; Pole, 2007; Shalev, Peri, Orr, Bonne, & Pitman, 1997). However, several other studies failed to find statistically significant differences between PTSD and non-PTSD comparison groups (Carson et al., 2007; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozaric-Kovacic, 2008; Metzger et al., 1999; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Orr et al., 2003; Siegelaar et al., 2006). Thus, potentially complicating the direct comparison of PPI results while PPI is not independent of baseline startle reaction (Csomor et al., 2008b).

In contrast to the conflicting findings of exaggerated startle and PPI, most (Ghisolfi et al., 2004; Gillette et al., 1997; Neylan et al., 1999; Skinner et al., 1999) but not all (Metzger et al., 2002) studies reveal reduced P50 suppression in PTSD patients.

Although an increasing number of studies have investigated neurophysiological alterations in patients with PTSD, the outcome provides a rather inconsistent and heterogenic picture of neurophysiological alterations in this disorder. Additionally, it remains widely unclear whether alterations of these neurophysiological measures in PTSD can be linked to specific psychopathological symptoms. Hence, the aim of the study reported in chapter 2 was firstly to characterise PTSD patients from a broader neurophysiological perspective by assessing sensory gating and sensorimotor gating in the same subjects under investigation, and second, to investigate the inter-relationship of these measures and a potential relation to psychopathological symptoms.

1.2.3. Sensory gating and sensorimotor gating in patients suffering from attention-deficit/hyperactivity disorder (ADHD)

ADHD is a serious mental disorder with an early onset and a persistent pattern of severely impaired attention and concentration, hyperactive and impulsive behaviour, emotional instability, restlessness, and disorganized behaviour (American Psychiatric Association, 2000). Although long perceived as a disorder in children, ADHD symptoms persist in adulthood (Barkley, 1990; Mannuzza, Klein, & Addalli, 1991; Weiss, Hechtman, Milroy, & Perlman, 1985) including cases with partial remission (Faraone, Biederman, & Mick, 2006). The prevalence rate of ADHD in children ranges from 3 to 12% (Barkley, 1990; Biederman & Faraone, 2005), in adults who meet full criteria for ADHD from 1 to 4% (Kessler et al., 2006; Faraone, Sergeant, Gillberg, & Biederman, 2003). Follow-up studies have found that up to 66% of children with ADHD showed a persistence of symptomatology in adulthood (Biederman et al., 1993; Kessler et al., 2006). Furthermore, the severity of adult ADHD disorder is underlined by high comorbidity rates in affective disorders, anxiety disorders, substance use disorders and personality disorders (Biederman, 2004; Shekim, Asarnow, Hess, Zaucha, & Wheeler, 1990; Spencer, Biederman, & Mick, 2007). Moreover, adults with ADHD disorder have lower educational status, higher risk for unemployment, divorce, or imprisonment, giving an important role to an effective treatment of ADHD (Wilens, Faraone, & Biederman, 2004). Moreover, ADHD is a multifactorial and clinically heterogeneous

disorder, associated with tremendous financial burden, stress to families, and adverse academic and vocational outcomes. Therefore, the importance to treat ADHD consequently with effective therapy adults is underlined by social factors, as patients with ADHD disorder have a lower educational status, a higher risk for unemployment, divorce, or imprisonment (Wilens et al., 2004).

Deficient information processing and impaired perceptual capacity in ADHD patients is thought to result in sensory overload which in turn may underlay ADHD symptoms, e.g. the inability to volitionally regulate attention and to constrain distraction (Armstrong, Hayes, & Martin, 2001; Spencer et al., 2007). A failure to inhibit irrelevant cognitive stimuli is consistent with the tendency of individuals with ADHD to switch prematurely from relevant to irrelevant cognitive processes (Armstrong et al., 2001).

In contrast to the findings in other psychiatric disorders reported in chapter 1.2., it is not yet established, if gating functions are impaired in ADHD patients. Furthermore, patients suffering from ADHD report to be over flooded with sensory input and exhibit deficits in comparable cognitive domains as the above mentioned disorders (Biederman, 2005; Faraone et al., 2000). Moreover, the few studies investigating sensorimotor gating functions in ADHD patients revealed no differences between patients and healthy controls (Feifel et al., 2009; Hanlon et al., 2008), except when attention is directed to the prepulse stimuli (Hawk, Jr., Yartz, Pelham, Jr., & Lock, 2003) or when the ADHD is accompanied by a tic disorder or primary nocturnal enuresis (Castellanos et al., 1996; Ornitz, Hanna, & de Traversay, 1992; Ornitz et al., 1999). The only study that explored P50 suppression in ADHD patients compared to healthy controls reported no significant differences (Olincy et al., 2000). So far, no study has investigated PPI and P50 in the same cohort of patients suffering from ADHD. Moreover, cognitive impairment is a common finding in the population of ADHD patients (Dinn, Robbins, & Harris, 2001; Murphy, 2002; Ossmann & Mulligan, 2003). While impaired cognition and deficient gating seem to be at least partly associated in schizophrenia spectrum disorders (Geyer, 2006a; Ludewig et al., 2003; Scholes & Martin-Iverson, 2009), studies investigating both forms of gating and cognitive performances as well as their inter-relationships are still lacking in ADHD research. Based on the reported findings of other patient groups and in ADHD research, a primary aim of the study reported in chapter 3 was to investigate two different forms of gating and their potential relationships to psychopathology of ADHD.

1.3. Pharmacological interventions on sensory gating and sensorimotor gating in schizophrenia research

About 1% of the population is suffering from schizophrenia, a grievous and heterogeneous mental disorder with a devastating influence on personal, familial, social and vocational facets of patients' lives and their relatives' lives. In the last years several approaches investigating neurophysiological and neuropsychological markers showed great promise for a better understanding of schizophrenia spectrum disorders characterized by an altered information processing. In regard to the pathophysiology of the miscellaneous cognitive deficits observed in schizophrenia there is increasing evidence that schizophrenia patients exhibit functional deficits in different domains of early information processing, e.g. sensory gating and sensorimotor gating deficits (Braff et al., 2001; Light & Braff, 1999). Furthermore, it has been proposed that PPI and P50 suppression are endophenotypic markers for schizophrenia spectrum disorders (Braff & Light, 2005; Cadenhead et al., 2002), and that gating measures provide a opportunity to investigate the effect of novel antipsychotic compounds (Geyer et al., 2001). Moreover, there is great evidence that atypical antipsychotic medication ameliorate sensory gating and sensorimotor gating in schizophrenic patients (Adler et al., 2004; Vrim-Ucok, Keskin-Ergen, & Ucok, 2008). While there might be a different impact on the two gating measures in-between the group of typical antipsychotics (Wynn et al., 2007), there is connotatively confirmation that atypical compared to typical antipsychotic medication may have a superior restorable effect on sensorimotor and/or sensory gating (Becker et al., 2004; Kumari, Soni, & Sharma, 1999; Kumari, Soni, Mathew, & Sharma, 2000; Kumari & Sharma, 2002; Leumann, Feldon, Vollenweider, & Ludewig, 2002; Light, Geyer, Clementz, Cadenhead, & Braff, 2000; Oranje, Van Oel, Gispen-De Wied, Verbaten, & Kahn, 2002; Swerdlow et al., 2006b; Vollenweider, Barro, Csomor, & Feldon, 2006).

Furthermore, in order to bridge the gap between basic and clinical research, the effect of antipsychotic medications on gating functions may be investigated in healthy volunteers exhibiting low levels of gating, rather than in patients. Given that PPI and P50 gating can be induced in healthy volunteers, we have developed a translational model to investigate the possible differential effects of antipsychotic medication on PPI and P50 suppression in healthy human subjects exhibiting low baseline gating, saving both resources and time (Csomor et al., 2008a; Vollenweider et al., 2006). Moreover, studying healthy subjects with or without pharmacological challenge has the potential to overcome the problem of confounding effects of previous medication exposure in patient populations. Studies with healthy volunteers can

overcome the wide range in severity of psychopathology and the generally non-random allocation of patients to treatment regimens (Hamm, Weike, & Schupp, 2001; Kumari & Sharma, 2002), which all can be a considerable source of variability.

Relating to the possible affected neurotransmitter systems in schizophrenia spectrum disorders, animal and human studies have shown that PPI can be modulated by dopaminergic, serotonergic, and glutamatergic interventions (Braff et al., 2001; Swerdlow, Braff, & Geyer, 2000). Much less is known for the involvement of the mentioned neurotransmitter systems in P50 suppression.

Recently an increasing number of studies have been published investigating the effect of antipsychotic medications on gating functions in healthy volunteers. Clozapine, as well as quetiapine, both with a mixed dopaminergic and serotonergic antagonistic mechanism, increase PPI in healthy subjects exhibiting low baseline PPI (Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006c; Vollenweider et al., 2006) while the typical antipsychotic haloperidol does not have an enhancing effect on PPI in healthy subjects with low sensorimotor gating (Csomor et al., 2008a). Furthermore, miscellaneous effects of haloperidol, a selective dopaminergic D_2 receptor antagonist, have been reported. In contrast to some studies, which found no effect (Abduljawad, Langley, Bradshaw, & Szabadi, 1999; Graham, Langley, Bradshaw, & Szabadi, 2001; Graham, Langley, Balboa Verduzco, Bradshaw, & Szabadi, 2002; Graham et al., 2004; Kumari et al., 1998; Liechti, Geyer, Hell, & Vollenweider, 2001), haloperidol attenuates PPI generally (Abduljawad, Langley, Bradshaw, & Szabadi, 1998; Oranje, Kahn, Kemner, & Verbaten, 2004) and attenuates PPI in high PPI subjects (Csomor et al., 2008a). Moreover, chlorpromazine, a potent D_2 receptor antagonist, has also no effect on PPI in healthy volunteers (Barrett, Bell, Watson, & King, 2004). In sum there is increasing evidence that mixed D_2 / 5-HT_2 receptor antagonists modulates PPI in a way to enhance PPI in subjects with low baseline gating while only D_2 receptor antagonists are without an effect on, or tend to attenuate, PPI in healthy volunteers.

In regard to P50 suppression, much less studies investigating the effect of antipsychotic medication in healthy volunteers have been published. Therefore, a combination of haloperidol and ketamine conduct to a decrement of P50 suppression whereas the application of ketamine did not affect P50 suppression (Oranje, Gispen-De Wied, Verbaten, & Kahn, 2002). Furthermore, haloperidol increases P50 suppression in subjects exhibiting low P50 gating while it disrupts P50 suppression in subjects with high P50 gating (Csomor et al., 2008a).

1.3.1. The effect of the antipsychotic sertindole on sensory gating and sensorimotor gating in healthy volunteers

Sertindole (Serdolect®), a potent antagonist at dopamine D_2, serotonin $5HT_{2A}$ receptors and α1-adrenoceptors, is a second-generation antipsychotic recently reintroduced in the market after a reevaluation of its safety, risks, and benefits (Lancon, Toumi, Sapin, & Hansen, 2008; Peuskens, Moore, Azorin, Toumi, & Cochran, 2007; Spina & Zoccali, 2008; Azorin, Murteira, Hansen, & Toumi, 2008). Although no study investigated the effect of sertindole on PPI or P50 suppression in humans, there is evidence from experiments with rodents that sertindole has the potential to increase PPI (Depoortere, Perrault, & Sanger, 1997; Paabol Andersen & Pouzet, 2001). Furthermore, studies with other antipsychotics as clozapine (Vollenweider et al., 2006) and quetiapine (Swerdlow et al., 2006c), which have both a preferential antagonistic activity at D_2- and $5HT_{2A}$-receptors, showed the potential to enhance PPI in healthy subjects with low baseline gating. Moreover, sertindole shares certain mechanisms of action (dopamine-D_2 and serotonin-$5HT_{2A}$ antagonistic action) with clozapine and quetiapine (Hertel, 2006) making it a potent candidate for translational gating research in healthy volunteers. Furthermore, due to its receptor profile (sertindole seems to have no or only small effect on muscarinic or histaminic H_1 receptors) and compared to other antipsychotic medication, sertindole is not linked with anticholinergic side effects and is less associated with sedation while still having a satisfactory antipsychotic effect on both, positive and negative symptoms (Arnt & Skarsfeldt, 1998; Kasper, Hale, Azorin, & Möller, 1999; Kasper, 2008; Perquin & Steinert, 2004; Zimbroff et al., 1997). Moreover, its favorable cognitive profile is proved in studies with rodents (Didriksen, 1995; Didriksen, Kreilgaard, & Arnt, 2006; Didriksen, Skarsfeldt, & Arnt, 2007; Rodefer, Nguyen, Karlsson, & Arnt, 2008; Skarsfeldt, 1996). Hence, the aim of the study reported in chapter 4 was to investigate the influence of sertindole by use of our translational model in healthy volunteers.

1.3.2. The effect of the antipsychotic sertindole on cognition and a potential relation between gating functions and impaired cognitive performances

Cognitive deficits in schizophrenia spectrum disorders, especially measured by (pre)frontal tasks and confirmed by a altered neuronal activity, is a undisputable finding (Badcock, Michiel, & Rock, 2005; Hutton et al., 1998; Manoach, 2003; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Weickert et al., 2000) with great impact on quality of life and

functional outcome (Brekke, Kay, Lee, & Green, 2005; Green, 2006). Moreover, recent findings suggest a relation between low levels of gating (PPI) in human volunteers with an impaired performance in tasks relying on the integrity and efficiency of specific cognitive domains relying on prefrontal cortical functioning (Bitsios, Giakoumaki, Theou, & Frangou, 2006; Csomor et al., 2008a; Giakoumaki, Bitsios, & Frangou, 2006). Furthermore, subjects with low compared to subjects with high PPI significantly differ in their performance in the spatial working memory (SWM) and planning task (SOC) of the Cambridge Neuropsychological Test Automated Battery (CANTAB), indicating that subjects with low baseline gating perform worse in these tasks (Csomor et al., 2008a). Therefore, the assumption of a presumable role of the prefrontal cortex in the modulation of PPI, which is supported from animal studies (Swerdlow et al., 2000; Swerdlow et al., 2001a; Swerdlow, Weber, Qu, Light, & Braff, 2008), is subsidized by the different performance of high and low baseline PPI subjects in domains of spatial working memory and planning (Csomor et al., 2008a). Furthermore, it can be assumed that superior ability in cognitive performance in these two domains is related to more efficient early information processing.

While the superior effect of potent $5HT_2$ (and relatively weaker D_2) antagonists on cognitive function has been discussed for longer (Meltzer & McGurk, 1999), further evidence of a better impact on cognitive functions of sertindole compared to haloperidol is coming from a study in schizophrenic patients (Gallhofer et al., 2007). Therefore, it has been discussed recently that the antagonistic activity at $5\text{-}HT_6$ receptors of sertindole might play a part in contributing a positive cognitive profile (Dawson, Nguyen, & Li, 2001; Hirst et al., 2006; King, Marsden, & Fone, 2008; Lacroix, Dawson, Hagan, & Heidbreder, 2004; Marcos, Chuang, Gil-Bea, & Ramirez, 2008; Meltzer, 1994; Miguel-Hidalgo, 2001; Rodefer et al., 2008; Schaffhauser et al., 2009; Singer et al., 2009; Upton, Chuang, Hunter, & Virley, 2008; Woolley, Marsden, & Fone, 2004). Although a cognitive enhancing effect cannot be expect from antipsychotic medication given to healthy volunteers, a prominent decline in cognitive performance as seen with other typical or atypical antipsychotic medication (Csomor et al., 2008a; McCartan et al., 2001; Vollenweider et al., 2006) might not be induced by sertindole. To this end, the aim of the study reported in chapter 4 was to investigate the effect of a moderate dose of sertindole compared to placebo on sensory gating and sensorimotor gating, cognitive performance, and psychopathological measures within the same cohort of healthy volunteers, and to further certify our current translational model.

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P50 Suppression, Prepulse Inhibition, and Startle Reactivity in the Same Patient Cohort Suffering from Posttraumatic Stress Disorder

Dominique H. Holstein, Franz X. Vollenweider, Lutz Jäncke,
Christian Schopper, and Philipp A. Csomor
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Abstract

Background: Psychophysiological alterations like impaired gating and increased startle have been reported in patients with posttraumatic stress disorder (PTSD). However, findings are inconsistent, and potential relationships to symptomatology remain unclear.

Aims: The present study investigates two distinct operational measures of gating and startle reactivity within the same patients suffering from PTSD and their relationship to PTSD symptomatology.

Methods: Prepulse inhibition of the acoustic evoked startle reflex, P50 suppression of auditory event related potentials, and startle reactivity were assessed in three distinct experiments in 27 PTSD patients and compared to 25 healthy control subjects.

Results: PTSD patients exhibited impaired P50 suppression and exaggerated startle. Lower P50 suppression was associated with higher levels of general psychopathology. Patients and control subjects did not differ in PPI.

Limitations: Some of the limitations include, that the control group compromised of non-trauma exposure subjects and menstrual cycle in female participants potentially affecting PPI was not controlled.

Conclusions: Deficient P50 gating, not related to specific trauma or distinct symptom clusters reflects a robust finding in PTSD patients. In contrast, further research is needed to clarify whether PPI is affected in PTSD.

Keywords: PTSD, PPI, startle, P50 suppression, gating

Introduction

Exposure to an intensely distressing traumatic event can trigger long-lasting behavioural changes contributing to the development of Posttraumatic Stress Disorder (PTSD). Three major symptoms are described as being characteristically for PTSD: on a mental and behavioural level there are intrusion and flashbacks to the traumatic event and avoidance of stimuli associated with the trauma. On a physiological level alterations such as persistent hyperarousal upon exposure to events relating to the traumatic event, hypervigilance and insomnia have been repeatedly reported in PTSD patients (Yehuda, 2004), and reflect specific criterions for the diagnosis of PTSD (American Psychiatric Association, 2000). Moreover, patients exhibit disturbed perceptual modulation, distractibility and lack of concentration (Stewart & White, 2008). Clinical observations supporting an association between exposure to life-threatening events and altered physiologic arousal have made trauma-related disorders obvious targets for neurophysiological assessment (Metzger et al., 2002; Orr, Metzger, & Pitman, 2002). It has been considered that disturbances in early information processing might underlie PTSD symptomatology, but the association with specific symptoms remains unclear (Stewart & White, 2008).

A fundamental feature of early information processing is the ability to inhibit, filter out, or gate extraneous stimuli and to attend to salient features of the environment. Suppression of the P50 auditory event related brain potential (P50 suppression) and prepulse inhibition (PPI) of the acoustic startle response are operational measures of sensory and sensorimotor gating. Deficient P50 suppression and PPI have been observed in a number of psychiatric conditions (Braff, Geyer, & Swerdlow, 2001; Light & Braff, 1999; Quednow, 2008). P50 gating is assessed by electroencephalographic (EEG) recording of auditory event related brain potentials (AEP) elicited by repeated pairs of auditory clicks. The first stimulus (S_1) not only produces an AEP approximately 50 ms after stimulation (P50 wave), but also activates gating processes, resulting in a suppression of the P50 AEP to the second stimulus (S_2). Similarly, PPI refers to the attenuation of the reflexive startle reaction elicited by an intense pulse stimulus when its presentation is shortly preceded (30–300 ms) by a weak prepulse stimulus (Graham, 1975; Hoffman & Ison, 1980). According to the 'protection of processing hypothesis' formulated by Graham (Graham, 1975; Graham, 1980; Graham, 1992), the inhibitory effect of the prepulse upon subsequent pulse processing reflects the protection of the ongoing processing of the antecedent prepulse against interference by the succeeding pulse. In practice, the magnitude of PPI is measured by the diminution of the startle response to the pulse stimulus due to the antecedent prepulse stimulus.

Although PPI and P50 suppression have not been assessed within the same patients suffering from PTSD, there is increasing evidence that PPI and P50 suppression represent different forms of gating. PPI and P50 gating do not correlate in healthy volunteers and schizophrenia patients (Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004; Light & Braff, 2001; Oranje, Geyer, Bocker, Leon, & Verbaten, 2006; Schwarzkopf, Lamberti, & Smith, 1993), although both have shown to be deficient in the same cohort of schizophrenia patients (Braff, Light, & Swerdlow, 2007).

Most (Ghisolfi et al., 2004; Gillette et al., 1997; Neylan et al., 1999; Skinner et al., 1999) but not all (Metzger et al., 2002) studies revealed deficient P50 suppression in PTSD patients, but the findings in regard to PPI are rather inconsistent. Impaired PPI has been reported in children with PTSD (Ornitz & Pynoos, 1989) and Vietnam veterans with PTSD (Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon, Morgan Ill, Davis, & Southwick, 1998a), but other studies could not replicate the finding of deficient PPI in patients suffering from PTSD (Butler et al., 1990; Grillon, Morgan, Davis, & Southwick, 1998b; Lipschitz et al., 2005). Consequently, the issue of whether PTSD patients exhibit impaired PPI remains unresolved.

Analogous to the conflicting results of startle modulation (i.e., PPI) studies investigating startle reactivity in PTSD patients report conflicting results in spite of the fact that exaggerated startle reflects a diagnostic criterion for the assessment of PTSD (DSM-IV criterion D5). Increased startle reactivity indicating a state of hyperarousal has been reported in patients suffering from PTSD (Butler et al., 1990; Grillon et al., 1998b; Morgan Ill, Grillon, Southwick, Davis, & Charney, 1995; Orr, Lasko, Shalev, & Pitman, 1995; Pole, 2007; Shalev, Peri, Orr, Bonne, & Pitman, 1997). However, several other studies failed to show differences in startle reactivity between PTSD patients and healthy controls (Carson et al., 2007; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozaric-Kovacic, 2008; Metzger et al., 1999; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Orr et al., 2003; Siegelaar et al., 2006), and even diminished startle has been reported (Ornitz & Pynoos, 1989). Although a part of the literature is based on the assumption that PPI is independent of the baseline startle reaction, there is accumulating evidence that argues against such an independency (Csomor et al., 2006; Csomor et al., 2008; Sandner & Canal, 2007; Yee, Chang, Pietropaolo, & Feldon, 2005). Therefore, the divergent results with regard to startle reactivity might have at least partly accounted for the conflicting findings in relation to PPI, thus potentially complicating the direct comparison of results between studies dealing with sensorimotor gating.

Given the inconsistent findings for early information processing, the primary aim of the present study was to investigate different forms of gating and startle reactivity and their potential

relationship to PTSD symptomatology. To this end, sensory and sensorimotor gating as indexed by P50 suppression and PPI, and startle reactivity were assessed within the same patients suffering from PTSD in comparison to healthy control subjects. Based upon the above summary of the available literature, we hypothesize that patients exhibit reduced P50 suppression, but not necessarily impaired PPI. Furthermore, we expect exaggerated startle reactivity in people with PTSD.

Methods and Materials

The study was approved by the ethics committee of Zurich canton and all subjects gave their informed written consent after being given complete explanation about the protocol and the purpose of the study. All subjects were instructed to abstain from drinking alcohol for at least 24 h before each test session, not to drink any caffeine-containing beverages on the day of testing, and to keep their usual smoking habits.

Participants and Experimental Design

Twenty-seven patients with PTSD, according to the Clinician-Admistered PTSD Scale (Current and Lifetime Diagnosis, CAPS-DX (Blake et al., 1995)) were recruited through the in- and outpatients service of the Psychiatric University Hospital Zurich. They were rated 7-14 days before the participation to the neurophysiological testing by a trained study independent psychiatrist. Trauma types potentially involved in the development of PTSD included sexual assault (n=7), physical assault (n=6), car accident (n=5), rape (n=4), emotional childhood abuse (n=4), and combat exposure (n=1). Some of the patients were taking antidepressant (SSRIs, n=5), anxiolytic (benzodiazepines, n=5), or neuroleptic (atypical antipsychotics, n=3) medication. Furthermore, 24 age and gender matched healthy volunteers were recruited by local advertisement and served as a comparison group. According to a psychiatric interview and screening using the DIA-X diagnostic expert system (Wittchen & Pfister, 1997) all participants were without a history or current presence of major psychotic and neurological disorders, and denied the use of illicit drugs. Furthermore, all healthy control subjects had no personal or family history of any psychiatric disorder. Patients completed the Impact of Event Scale-Revised (IES-R; Weiss & Marmar, 1996), the Beck Depression Inventory (BDI; Beck & Steer, 1987), the State-Trait-Anxiety-Inventory (STAI; Spielberger, Gorsuch, & Lusheme, 1970), and the Dissociation Experience Scale (DES; Bernstein & Putnam, 1986). Furthermore, all participants completed the Hopkins Symptom Checklist (SCL-90-R; Derogatis, 1977). The healthy control subjects were free of any medication for at least 3 weeks before the experiment.

On the experimental day subjects filled in the psychometric questionnaires, and hearing was evaluated using a pure tone (tone frequencies: 500, 1000, 2000, 4000, 6000 Hz) audiometer (Earscan 3, Micro Audiometrics Corp., NC, USA). None of the patients but one control subject was excluded due to hearing difficulties (hearing threshold > 30 dB_{HL}). Then, subjects underwent the startle experiment, the P50 suppression test session, and last the PPI assessment. Each of the electrophysiological recordings was separated by a short break of about 5 min.

Session Definitions

The P50 suppression test session was composed of 70 pairs of auditory clicks with a 500 ms interclick interval presented every 6–10 s (mean: 8 s). Stimuli consisted of 90 dB_A white noise with a duration of 1 ms. The session lasted for approximately 10 min.

The PPI test session was composed of a mixture of pulse-alone trials, prepulse-pulse trials, and trials in which no discrete stimulus other than the constant background noise was presented (denoted hereafter as 'NS trials'). All stimuli (background noise and pulses) used in the experiment consisted of broadband white noise. The intensity of the background noise was set at 70 dB_A. Pulse stimulus intensity was set at 115 dB_A and the prepulse stimulus intensity at 86 dB_A. All pulses were 40 ms in duration, and all prepulses were of 20 ms duration. Rise and fall time of the stimuli were less than 1 ms. The three stimulus onset asynchronies (SOA) between the prepulse and pulse stimuli on prepulse-pulse trials were 60, 120, and 2000 ms. The session began with a 2 min period of acclimatization to the background noise, followed by the presentation of 43 discrete trials according to a variable intertrial interval ranging from 8 to 18 s (mean: 12 s). The first and last block consisted of two consecutive pulse-alone trials. The middle block consisted of 35 trials, 7 trials of each of the 5 conditions (pulse-alone, prepulse-pulse combinations, and NS trials). The sequence of presentation was pseudo-randomized, and lasted approximately 11 min.

The startle test session was composed of pulse trials of four different intensities (85, 95, 105, and 115 dB_A) and NS trials. All stimuli used in the experiment consisted of broadband white noise. Background noise and stimulus duration for pulse stimuli and rise / fall time were identical as for the PPI experiment. The session began with a 2 min period of acclimatization to the background noise, followed by the presentation of 39 discrete trials according to a variable intertrial interval ranging from 10 to 20 s (mean: 15 s). The first 4 consecutive pulse trials (one of each intensity) were not taken into account in the statistical analysis as these trials served to stabilize the subject's startle response. The following trials consisted of 7 trials of each

intensity and NS trials resulted in a total of 35 trials. The sequence of presentation was pseudo-randomized, and lasted approximately 12 min.

Apparatus, Data Recording and Data Processing

All psychophysiological recordings were performed in the same soundproof EEG room. The subjects were informed that the startle and PPI experiment were intended to investigate simple blink reflexes in the presence of background noise, and that the P50 experiment was for the investigation of changes in brain activity upon auditory stimulation. They were informed that all stimuli applied do not pose any risk to their hearing. Subjects were then asked to sit comfortably in a chair, to relax, and stay awake while looking at a blank wall approximately 2 m away. Acoustic stimuli were generated by EMG-SR (San Diego Instruments, San Diego, CA, USA), and applied binaurally through headphones (TDH-39-P, Maico, Minneapolis, MN, USA). EEG recordings were made from 64 scalp locations (10–20 system) (Jasper, 1958) using the ActiveTwo system (Biosemi, The Netherlands). The horizontal electroocculogram (EOG) was recorded from electrodes attached on the outer canthus of each eye. Similarly, vertical EOG was recorded from electrodes attached infraorbitally and supraorbitally to the right eye. Additionally, startle reaction was assessed from two electrodes placed below the right eye over the orbicularis oculi muscle. All electrodes were active silver/silver chloride electrodes and the offset of all electrodes was below 25 mV. The system recorded continuously over the whole session using a sampling rate of 4096 Hz for the startle and PPI paradigms, and 512 Hz for the P50 paradigm. For post-processing of the EEG and EMG data, BrainVision Analyzer software (Brainvision, Germany) was used.

For the P50 suppression paradigm, data were band-pass filtered (10–70 Hz, 50 Hz notch filter). Independent component analysis was used to remove artifacts due to eye movements and blinks. EEG data were re-referenced to the average of the 64 scalp electrodes (average reference) and segmented from 500 ms before to 1000 ms after the first click resulting in 70 segments. Resulting segments were visually screened for any sign of corrupted EEG and, if present, excluded from further processing. The artifact-free segments were then re-segmented 100 ms before click onset to 250 ms after click onset separately for both stimulus conditions (S_1 and S_2) and then averaged. The P50 component of the AEP was identified and scored as described by Nagamoto, Adler, Waldo, and Freedman (1989). The P50 peak was identified as the most positive deflection 40–80 ms after stimulus presentation. The P50 amplitude was scored as the absolute difference between the P50 peak and the preceding negative trough.

Only data from the Cz location were analyzed where the maximum activity for the P50 AEP was expected (Clementz, Geyer, & Braff, 1998).

For the startle and PPI paradigm, the two electrodes located over the orbicularis oculi muscle were referenced bipolarly, resulting in a single EMG channel. EMG activity was band-pass filtered (30–500 Hz), downsampled to 1000 Hz to reduce the amount of data, and then rectified. Segmentation was performed from 50 ms prior to the onset of the relevant stimulus (for PPI paradigm the prepulse in prepulse-pulse trials, respectively the pulse in pulse-alone trials and for the startle paradigm the pulse), and lasted to 2300 ms after stimulus onset for the PPI paradigm, and to 450 ms for the startle paradigm. The segmented data were exported for quantitative analysis. The EMG record of each and every trial was separately scored using the Windows®-based software emgBLINK version 1.2 (CST, Switzerland). Before scoring, the EMG was smoothed with a time constant of 5 ms. Baseline amplitude was calculated by the mean response amplitude of the first 50 ms before any stimulus onset. Stimulus response amplitudes were assessed as peak response minus baseline value of the respective trial. Peak response was defined as the highest reaction in the time window between stimulus onset and 150 ms after stimulus onset. Response amplitudes on NS trials were scored as peak response sample between 51 and 201 ms minus baseline value of the respective trial. Every trial was also examined for signs of spontaneous eye blinks in the scoring windows, and other possible signs of corrupted EMG signal, and if present the trial was excluded.

Assessed Parameters

The following electrophysiological measures were assessed. P50 suppression paradigm: *P50 amplitude* and *latencies* evoked by S_1 and S_2. *%P50 suppression* according to the formula: [1-(amplitude$_{s2}$)/(amplitude$_{s1}$)] x 100%. PPI paradigm: Pulse-alone elicited *startle* separately for each of the three blocks of the testing session, and mean reactivity score obtained on NS trials. *%PPI* calculated for each SOA by the formula: [1-(amplitude$_{\text{prepulse-pulse(block2)}}$) / (amplitude$_{\text{pulse-alone(block2)}}$)] x 100%. %Habituation of the startle reaction between the first and last block according to the formula: [1-(amplitude$_{\text{pulse-alone(block3)}}$) / (amplitude$_{\text{pulse-alone(block1)}}$)] x 100%. Startle paradigm: Mean *startle reactivity* elicited by the 2nd to the 8th pulse stimulus, separately for each of the 4 different intensities, and mean reactivity score obtained on NS trials. *%Habituation* between the mean startle magnitude elicited by the 2nd to the 4th trial and the 6th to the 8th trial of each intensity condition by the formula: [1-(amplitude$_{\text{trial6-8}}$) / (amplitude$_{\text{trial2-4}}$)] x 100%.

Statistical Analysis

All statistical analyses were conducted using Statistica 7.1 for Windows (Statsoft Inc., OK, USA).

Distributions of the startle and P50 amplitudes were highly positively skewed ($p_{Shapiro\text{-}Wilk\ W} < 0.001$ for all conditions). Even though parametric analysis of variance (ANOVA) can tolerate deviations from the normality assumption, enhanced compliance to it, which often also results in homogeneity of variance, improves considerably statistical power (Levine & Dunlap, 1982; Bland & Altman, 1996). After ln-transformation, startle and P50 amplitudes did not deviate significantly from normality ($p_{Shapiro\text{-}Wilk\ W} > 0.05$ for all conditions). While statistical comparisons of pulse-alone elicited startle reactivity was based using ln-transformed startle data, the calculation %PPI and %P50 suppression was based on non-transformed startle data. Amplitude and latency of the P50 component were analyzed separately by two-way ANOVAs with the factors 'stimulus type' (S_1 vs S_2) as within subject factor, and 'group' (patients vs controls) as between subject factor. The %P50 suppression data and peak latency were analyzed separately by one way ANOVAs.

For PPI paradigm startle was analyzed with the factor 'block' (1 to 3) as within- and 'group' as between-subject factor. %PPI values derived from the inhibitory SOAs (60, 120 ms) were subjected to a 2 x 2 (SOA x group) repeated measures ANOVA. Additionally, analysis of prepulse facilitation (PPF) (SOA: 2000 ms) and %habituation was analyzed by a one way ANOVA.

Startle reactivity in the startle paradigm was analyzed using repeated measures ANOVA with 'intensity' (5 levels: NS, 85, 95, 105, 115 dB_A) as within-subject factor and 'group' as between-subject factor. The analysis of %habituation using a 2 x 4 (group x pulse intensity) repeated measures ANOVA, although the most fitting and appropriate ANOVA design according to the session definition, turned out to be suboptimal for the analysis of the present data set, because only 14 subjects (9 patients, 5 controls) exhibited reliable startle reaction in regard to the $85dB_A$ stimulus condition, which was also the case for only 25 subjects (13 patients, 12 controls) in regard to the $85dB_A$ intensity condition. However, a reliable startle reaction at the beginning of the testing session is a prerequisite for a meaningful calculation of %habituation. Therefore, habituation was analyzed by a 2 x 2 (group x pulse intensity) repeated measures ANOVA only including the 105 and 115 dB_A conditions, under exclusion of only 9 subjects (5 patients, 4 controls) lacking reliable startle toward the 105 dB_A pulse stimulus.

Potential commonalities between neurophysiological parameters and the psychopathological ratings (SCL-90, CAPS-DX, IES, STAI, BDI and DES) were investigated by Pearson correlations. For all the statistical tests the significance level was set to $p < 0.05$. For post hoc testing Fisher's least significant difference (LSD) was used. In the case of significant effects, the effect size expressed as partial eta-squared η_p^2 was calculated.

Results

Psychometric data

IES-R data from three patients, BDI data from two patients, and STAI, SCL-R 90 and DES data from one patient were missing. As summarized in Table 1, PTSD patients and the healthy volunteers did not differ in age, gender, smoking habits, and alcohol consumption. As expected, patients and control subjects differed in the three SCL-90-R global indices Global Severity Index (GSI), Positive Symptom Total (PST), and Positive Symptom Distress Index (PSDI), indicating higher symptom severity in the patients. Diagnostic characteristics are summarized in Table 2.

Table 1: Demographic and SCL-90-R characteristics of the patients and control subjects

	Patients		Controls		Main effect of group		
	Mean	SE	Mean	SE	F	p	η_p^2
Gender							
Males	7		5				
Females	20		19				
Age [y]	39.96	2.13	37.38	2.27	< 1	n.s.	
Nicotin consumption [cigarettes/day]	7.19	2.48	5.17	1.83	< 1	n.s.	
Alcohol consumption [units/week][a]	3.24	0.89	6.04	1.27	3.38	0.07	
SCL-90-R (n_p=26/n_c=24)							
PST score	62.39	3.52	11.5	1.61	**163.51**	**<0.001**	**0.77**
GSI score	1.65	0.15	0.16	0.03	**86.74**	**<0.001**	**0.64**
PSDI score	2.27	0.12	1.22	0.05	**64.11**	**<0.001**	**0.57**

Note: SE, standard error; SCL-90, Symptom Check List; PST, Positive Symptom Total; GSI, Global Severity Index; PSDI, Positive Symptom Distress Index; n_p, number of patients; n_c, number of controls.

[a]1 unit = 1dl wine, or 3dl beer, or 4cl hard liquor

Table 2: Diagnostic characterisitcs of the patients

	Mean	SE
CAPS (n_p=27)		
Total score	68.42	3.92
Reexperiencing	19.67	1.84
Avoidance/Numbing	26.50	1.99
Arousal	22.25	1.51
IES (n_p=24)		
Sum score	0.40	0.32
Intrusion	20.79	1.95
Avoidance	23.08	2.10
Hyperarousal	23.75	1.62
STAI (n_p=26)		
State	54.54	2.65
Traite	57.23	2.23
BDI (n_p=25)		
Sum score	24.08	2.34
DES (n_p=26)		
Sum score	0.18	0.03

Note: SE, standard error; CAPS, Clinical-Admistered PTSD Scale; IES, Impact of Event Scale; STAI, State-Trait-Anxiety Inventory; BDI, Beck Depression Inventory; DES, Dissociation Experience Scale; n_p, number of patients.

P50 Suppression Paradigm

The P50 suppression data of four patients and five control subject were rejected because no distinct P50 component elicited by S_1 could have been identified.

As shown in Table 3 patients exhibited significantly less %P50 suppression compared to the control group. Analysis of P50 amplitudes revealed a significant main effect of 'stimulus type', confirming the occurrence of P50 suppression. Moreover, the interaction between the factors 'stimulus type' and 'group' attained significance. Post-hoc testing revealed that the amplitude elicited by S_1 did not significantly differ between patients and controls, while the amplitude evoked by S_2 was significantly higher in the patients ($p < 0.05$). No significant effects were detected in the analysis of P50 latencies.

Prepulse Inhibition Paradigm

Three patients refused to complete the PPI assessment, and data of six patients and six healthy subjects were rejected as no distinct startle reaction was elicited by pulse-alone stimuli (non-responders, mean startle amplitude <10 μV in the presentation block relevant for %PPI calculation). As summarized in Table 3, patients and controls did not differ in %PPI or %habituation. Neither the factor 'SOA', nor the 'SOA' x 'group' interaction attained significance. Similarly, startle amplitudes elicited by pulse-alone stimuli did not differ between the two groups, but as expected, startle amplitude diminished over the three blocks of the testing session.

Table 3: Electrophysiological characteristics of the P50 Supression and PPI experiment

	Patients		Controls		Main effect of of group			Main effect of within-subject factor (stimulus type | block | SOA)		
	Mean	SE	Mean	SE	F	p	η_p^2	F	p	η_p^2
P50 suppression (n_p=23/n_c=19)										
Amplitudes [µV][a]					1.52	n.s.		**35.29**	**<0.001**	**0.47**
S1	0.11	0.18	0.22	0.14						
S2	-0.48	0.18	-1.28	0.39						
Suppression (%)	28.15	9.94	66.50	4.09	**10.99**	**<0.01**	**0.22**			
Latency [ms]					< 1	n.s.		< 1	n.s.	
S1	56.05	0.91	58.49	1.10						
S2	58.42	1.93	57.77	1.42						
PPI (n_p=18/n_c=18)										
Startle amplitude [µV]					< 1	n.s.		**14.04**	**<0.001**	**0.30**
Block 1	4.22	0.18	4.37	0.16						
Block 2	3.88	0.20	4.04	0.15						
Block 3	3.50	0.20	3.88	0.25						
Habituation [%]	42.16	8.76	10.21	17.60	2.55	n.s.				
Inhibition [%]					2.31	n.s.		2.39	n.s.	
SOA 60 ms	50.46	6.28	58.82	5.51						
SOA 120 ms	52.22	7.96	67.94	4.15						
Facilisation [%]										
SOA 2000 ms	1.36	11.02	1.27	8.45	< 1	n.s.				

Note: SE, standard error; S1, first stimulus; S2, second stimulus; PPI, prepulse inhibition; SOA, stimulus onset asynchrony; n_p, number of patients; n_c, number of controls.

[a]Significant "group" x "stimulus type" interaction [F(1,40)=6.86, p<0.05, η_p^2=0.15]

Startle Paradigm

The startle data of three patients and one healthy subject were rejected because of bad quality. Additionally, data from one patient had to be excluded from the analysis of %habituation due to bad data in the blocks used to index habituation. Compared to the control group PTSD patients exhibited significantly higher startle reactivity across the five stimulus conditions [$F(1,45) = 4.82$, $p < 0.05$, $\eta_p^2 = 0.10$]. Dunnett's test of the startle reactivity with the NS trials as control condition revealed that the patients startle reactivity was significantly elevated for all stimulus intensities while in the control group this was only the case for the 105 and 115 dB_A conditions. As expected, there was a significant main effect of the factor 'intensity' [$F(4,180) = 177.36$, $p < 0.001$, $\eta_p^2 = 0.80$], but no significant 'group' x 'intensity' interaction (Fig. 1). Analysis of %habituation revealed no significant main effect of the factor 'group', 'intensity', or their interaction (%habituation, mean ± SE: 105 $dB_{A,\ patients}$ = 24.92 ± 7.88; 115 $dB_{A,\ patients}$ = 6.62 ± 6.82; 105 $dB_{A,\ controls}$ = 15.08 ± 7.39; 115 $dB_{A,\ controls}$ = 13.90 ± 7.02).

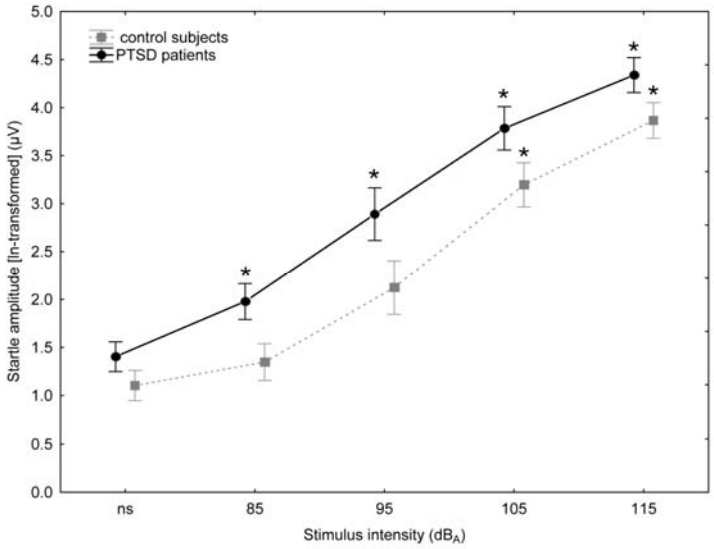

Figure 1. Startle reactivity (ln-transformed) of the PTSD patients and healthy control subjects. 'ns' refers to 70 dB_A background noise. '*' indicates significant difference in startle reactivity compared to the ns condition of the same group. Error bars refer to ± SE.

Correlative Analysis:

The negative correlations between %P50 suppression and the three global indices of SCL-90-R, related higher psychopathological indices to lower P50 gating performance (Global Severity Index: $r = -0.35$, $p < 0.05$; Positive Symptom Total: $r = -0.37$, $p < 0.05$; Positive Symptom Distress Index: $r = -0.33$, $p < 0.05$; Fig. 2). Any other correlation between neurophysiological measures (%P50 suppression, %PPI, startle, and startle habituation) and psychopathological indices (SCL-90, CAPS-DX, IES, STAI, BDI and DES scores) did not attain significance.

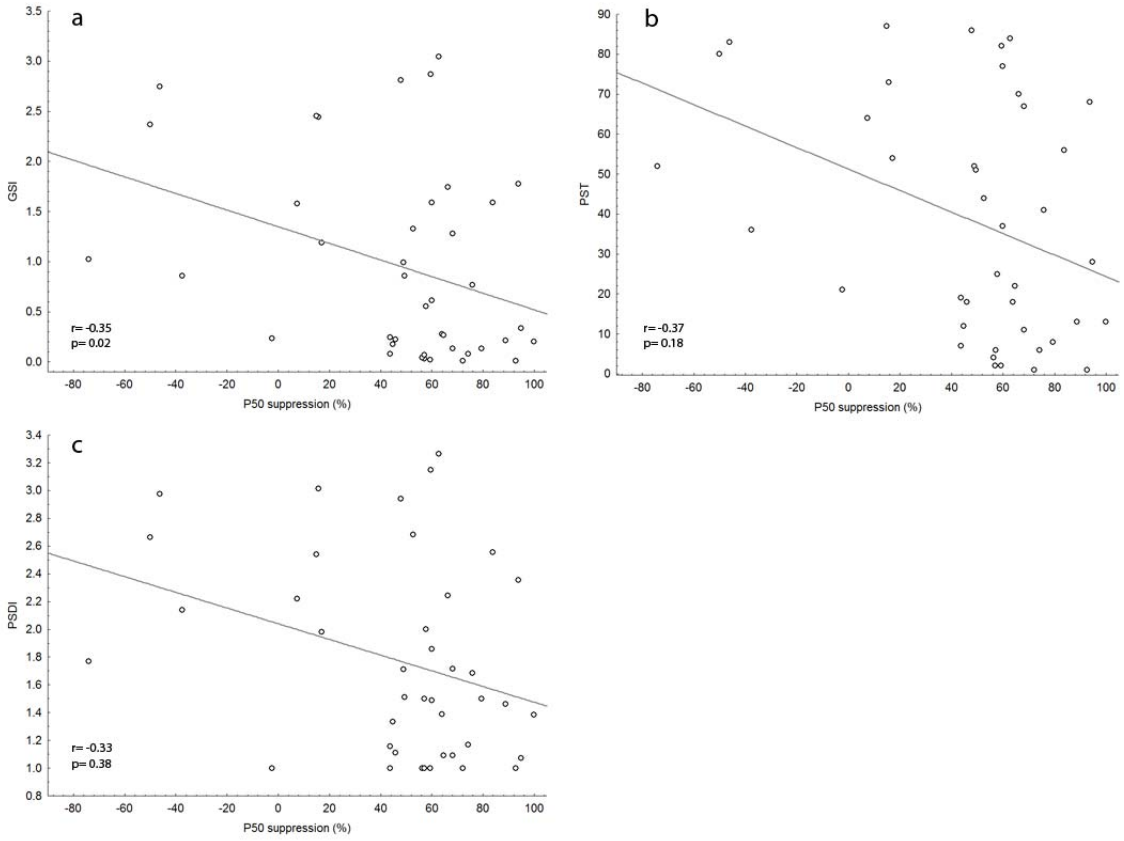

Figure 2. Correlations of percentage P50 suppression and the three SCL-90 global indices.

Discussion

To our knowledge this is the first study investigating PPI, P50 suppression and startle reactivity within the same PTSD patients. The current results revealed that PTSD patients exhibited impaired P50 suppression and exaggerated startle reactivity. On the other hand, PPI did not differ between patients and controls.

The present finding of impaired sensory gating as indexed by low P50 suppression in patients suffering from PTSD is in agreement with the majority of the past findings (Gillette et al., 1997; Ghisolfi et al., 2004; Karl, Malta, & Maercker, 2006; Neylan et al., 1999; Skinner et al., 1999). Consistent with a previous report (Metzger et al., 2002), higher SCL-90-R global scores were associated with lower P50 gating. However, the present results and the findings of Metzger et al. (2002) have to be interpreted with caution, since the correlations account only for a limited proportion of the variance (< 14%), and p-levels would suffer significance when adjusted for multiple comparison. It remains essential to further validate potential relationships

between general psychopathology and the magnitude of P50 gating in various patient cohorts including PTSD.

The present results show that PTSD patients did not exhibit diminished sensorimotor gating. In the domain of PTSD results of studies assessing PPI revealed conflicting results. While some studies reported impaired sensorimotor gating (Grillon et al., 1996; Grillon et al., 1998a; Ornitz & Pynoos, 1989), others could not detect deficient PPI (Butler et al., 1990; Grillon et al., 1998b; Lipschitz et al., 2005). Braff et al. (2001) assumed that differences in experimental parameters between laboratories contribute for these divergent results. Opposite to gating research in PTSD, experimental parameters used for PPI experiments in schizophrenia research are highly standardized between studies of different laboratories, which might partially account for the overwhelmingly number of investigations reporting deficient PPI in patients suffering from schizophrenia (Braff et al., 2001; Swerdlow et al., 2006; Swerdlow, Weber, Qu, Light, & Braff, 2008). Although stimulus parameters applied in the present study comply with the vast majority of PPI studies, no deficient sensorimotor gating was detected in the patients. Another source potentially complicating the comparability and interpretation of PPI between studies is inherent to potential differences in startle reactivity between groups under comparison. Changes in PPI with concomitant changes in startle amplitude cannot be directly interpreted as a change in sensorimotor gating per se (Braff et al., 2001; Csomor et al., 2008; Swerdlow, Braff, & Geyer, 2000). Although the present data set did not reveal differences in PPI between patients and controls, one could assume that divergent startle reactivity between the two groups potentially masked differences in %PPI. Even though startle reactivity was elevated in the startle testing session consisting of pulse stimuli only, no between-group difference in regard to startle reactivity was detected in the PPI session. Furthermore, systematic investigation of a potential relationship between startle reactivity and PPI has shown that high startle reactivity is associated with lower %PPI (Csomor et al., 2008). Thus, it can be safely concluded that the absence of a PPI difference between PTSD patients and healthy controls cannot be attributed to divergent startle reactivity between the two groups as indicated by the results derived from the startle testing session.

Stewart and coworkers (Stewart & White, 2008) showed that patients suffering from PTSD reported disruption in a self-reported assessment of sensory filtering. Although speculative, this might be reflected on a neurophysiological level by diminished P50 suppression in spite of the absence of deficient PPI as in the present study. Reduced P50 gating in the patients was due to differences in the amplitudes elicited by S_2, rather than S_1 and therefore can be interpreted as an impairment in central inhibitory activity (Ghisolfi et al., 2004; White & Yee, 1997). The

current finding adds evidence to previous reports (Braff et al., 2007; Brenner et al., 2004; Light & Braff, 2001; Oranje et al., 2006; Schwarzkopf et al., 1993) indicating that P50 gating and PPI represent distinct forms of gating which are not correlated with each other, as correlations coefficients derived from Pearson correlations between %PPI and %P50 were low and not statistically significant ($r_{SOA60} = 0.27$; $r_{SOA120} = 0.19$).

Deficient P50 suppression might be a potential promising candidate for an endophenotype marker in PTSD or the vulnerability to its development. Some of the criterions stated by (Gottesman & Gould, 2003), such as heritability and state-independency, qualifying P50 gating as an endophenotype candidate in PTSD are fulfilled (Anokhin, Vedeniapin, Heath, Korzyukov, & Boutros, 2007; Hall et al., 2006; Kisley et al., 2003; Kisley, Olincy, & Freedman, 2001). On the other hand, it must be investigated whether non-affected family members of PTSD patients do show reduced P50 gating at a higher rate than in the general population, and whether it is co-segregating within such families. Furthermore, one has to keep in mind that P50 suppression is not specific to the disorder as impaired P50 gating is frequently reported in other psychiatric conditions (Cadenhead, Light, Geyer, & Braff, 2000; Light & Braff, 1999; Martin et al., 2007; Schulze et al., 2007). That reduced P50 gating is not exclusively attributable to PTSD is also reflected by the association with general psychopathology as index by SCL-90 global scores, and the absence of such a relationship with PTSD specific symptomatology.

The present result of increased startle reactivity in PTSD patients is in agreement with previous reports (Butler et al., 1990; Grillon et al., 1998b; Morgan Ill et al., 1995; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Orr et al., 1995; Pole, 2007; Shalev et al., 1997). As habituation did not differ between patients and control subjects, the finding of increased startle cannot be attributed to low habituation in the patients. Similarly, Morgan III et al. (1995), Orr et al. (1995), and Shalev et al. (1997) found that differences in startle reactivity were not accompanied by diminished habituation. Furthermore, most of the studies investigating startle reactivity in PTSD found no difference in habituation between patients and controls (Carson et al., 2007; Grillon et al., 1996; Lipschitz et al., 2005; Metzger et al., 1999; Orr et al., 1997; Orr et al., 2003; Siegelaar et al., 2006), whereas a single investigation reported impaired habituation (Jovanovic et al., 2008). Thus, it can be concluded that exaggerated startle and diminished habituation, if any, reflect mostly independent neurophysiological alterations. That numerous studies failed to detect differences in startle reactivity between patients and controls (Carson et al., 2007; Grillon et al., 1996; Jovanovic et al., 2008; Metzger et al., 1999; Orr et al., 1997; Orr et al., 2003; Siegelaar et al., 2006), or even reported decreased startle (Ornitz &

Pynoos, 1989) seems to be paradoxically in the light of exaggerated startle is reflecting a DSM-VI diagnostic criteria for the assessment of PTSD (Sass, Wittchen, & Zaudig, 1998). These negative findings might be attributed to differences in experimental parameters to elicit startle. First of all, most of the studies revealing negative results made use of a single (Carson et al., 2007; Griffin, 2008; Jovanovic et al., 2008; Lipschitz et al., 2005; Medina, Mejia, Schell, Dawson, & Margolin, 2001; Metzger et al., 1999; Orr et al., 1997; Orr et al., 2003; Siegelaar et al., 2006) or two (Grillon et al., 1996) stimulus intensities only to evoke startle. Analogously, the present data set did not reveal startle differences between patients and controls when measured in the PPI paradigm where a single pulse stimulus intensity was applied, in spite of two studies revealing startle differences evoked by a single stimulus intensity (Orr et al., 1995; Shalev et al., 1997). The current findings underline the importance of including startle evoking stimuli of multiple intensities to enhance the likelihood for the detection of exaggerated startle in patients suffering from PTSD.

Another reason for the divergent findings of exaggerated startle in the patients measured in the startle testing session and the absence of such a startle difference in the PPI session might be inherent to the state anxiety and a general higher arousal level of the patients at the beginning of the test session. While startle reactivity elicited by 115 dB_A pulse stimuli dropped from 101 μV (non-transformed) in the startle experiment conducted at the beginning of the experimental procedure down to 68 μV (non-transformed) in the PPI session at the end of the neurophysiological assessment, the control subjects startle reactivity remained stable (68 μV in both paradigms, non-transformed). Patients might have become accustomed to the laboratory environment during the series of experiments, and consequently, elevated startle in the present PTSD sample would be state anxiety depended. In this connection, it has been shown that increased startle in PTSD patients has been consistently reported when elicited in settings in which the subject anticipate an aversive event (i.e., fear potentiated startle) (Grillon et al., 1998a; Grillon et al., 1998b; Grillon & Morgan, III, 1999; Medina et al., 2001; Morgan Ill et al., 1995).

Many studies investigating psychophysiological alterations in PTSD rely on relatively homogenous patient samples like male combat veterans (Butler et al., 1990; Gillette et al., 1997; Grillon et al., 1996; Grillon et al., 1998a; Grillon et al., 1998b; Grillon & Morgan, III, 1999; Jovanovic et al., 2008; Morgan Ill et al., 1995; Neylan et al., 1999; Orr et al., 1995; Orr et al., 1997; Orr et al., 2003; Skinner et al., 1999) or Vietnam nurses (Carson et al., 2007; Metzger et al., 2002). The PTSD symptomatology of the cohort studied in the present investigation is based on various traumatic experiences, and the three times higher lifetime

prevalence for females in European countries (Alonso et al., 2004) explains the unequal distribution between male and female patients. Therefore, the present findings of impaired P50 gating and increased startle in PTSD patients seem not to be trauma specific.

Some of the patients were medicated which might have influenced the current findings. SSRIs seem not to modulate PPI or startle reactivity (Jensen, Oranje, Wienberg, & Glenthoj, 2007), while the influence on P50 suppression remains to be empirically investigated. Benzodiazepines are known to diminish startle reactivity, and have no or reducing effect on PPI and AEP gating (Abduljawad, Langley, Bradshaw, & Szabadi, 1997; Abduljawad, Langley, Bradshaw, & Szabadi, 2001; Schachinger, Muller, Strobel, Langewitz, & Ritz, 1999). Atypical neuroleptics tend either to reduce or not affecting startle reactivity (Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006; Vollenweider, Barro, Csomor, & Feldon, 2006; Wynn et al., 2007), while on PPI and P50 suppression enhancing but not reducing effects have been reported (Adler et al., 2004; Kumari & Sharma, 2002; Vollenweider et al., 2006). Therefore, the present results of elevated startle and impaired P50 suppression cannot be attributed to potential drug effects present in some of the patients.

Limitations

The findings of the present study and its interpretation include some limitations. As the healthy control subjects were not trauma exposed limits the conclusion that PTSD per se accounts for the observed neurophysiological differences. Other studies included trauma exposed non-PTSD subjects as a comparison group allowing to control the factor of trauma exposure (Carson et al., 2007; Jovanovic et al., 2008; Metzger et al., 1999; Orr et al., 1997; Orr et al., 2003; Siegelaar et al., 2006).

A confounding not controlled factor in the present study was the menstrual cycle, which is known to affect PPI. Sensorimotor gating is lower in luteal phase compared to the follicular (Bannbers, Kask, Wikstrom, & Sundstrom, I, 2009; Jovanovic et al., 2004;).

That the control group was not asked to complete BDI, IES-T, STAI and DES questionnaires limits a possible association between psychopathological measures and neurophysiological outcomes in the present study.

Conclusion

Deficient P50 gating, not related to specific trauma or distinct symptom clusters reflects a robust finding in PTSD patients. Further research is needed to clarify whether P50 gating

might reflect an endophenotype marker for the vulnerability of that disease. In regard to PPI, it is imperative to establish firm experimental parameters enabling effective comparisons of results between different laboratories. Additional investigations are necessary, above all longitudinal studies to evaluate whether operational measures of gating and startle have the potential to serve as efficacy markers for therapeutic outcome or might even be instrumental as vulnerability predictors for the development of PTSD following traumatic experience.

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Sensory and sensorimotor gating in adults suffering from Attention-deficit/hyperactivity disorder (ADHD)

Dominique H. Holstein, Franz X. Vollenweider, Mark A. Geyer,
Phillip A. Csomor, Nadine Belser, Dominique Eich
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Chapter 3 is based on a paper submitted for publication in the Journal of Affective Disorders, and consists of original works that I have contributed and participated directly including the design of experiments, collection of data, statistical analysis, and the preparation of the final manuscript, with the additional contributions by Prof. Vollenweider, Prof. Geyer, Dr. Csomor, Ms. Belser, and Prof. Eich, who appear as co-authors in the published paper.

Abstract

Background: Even though there is an impaired perceptual capacity in attention-deficit/hyperactivity disorder (ADHD) patients, psychophysiological alterations, such as impaired gating as indexed by prepulse inhibition of the startle response (PPI) or condition-test suppression of P50 auditory event-related potentials, have not been reported in patients suffering from ADHD. Hence, potential relationships of psychophysiological measures of gating to psychopathology and cognitive performance remain unclear.

Aims: The present study investigates two distinct operational measures of gating as well as cognitive performance within patients suffering from ADHD in order to assess the relationship of these measures to psychopathology.

Methods: PPI, P50 suppression, cognitive performance measured by a subset of tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB), and psychopathologic rating scales were assessed in three distinct experiments in 26 ADHD patients and 26 healthy control subjects.

Results: ADHD patients exhibited impaired P50 suppression, performed worse in cognitive tasks, and reported more psychopathological symptoms, but were normal in the test of PPI.

Limitations: Some of the limitations include, that menstrual cycle in female participants potentially affecting PPI was not controlled, and that the majority of ADHD patients participating in the present study were diagnosed with the combined type, limiting the conclusions made to the mentioned ADHD subtype.

Conclusions: The present results extend the differences between P50 gating and PPI as measures of the gating construct. In keeping with the lack of correlations between these two putative operational measures of gating seen in both humans and animals, patients with ADHD exhibit deficient P50 suppression and poor cognitive performance, despite exhibiting normal levels of PPI. Thus, P50 gating deficits are not specific to schizophrenia spectrum disorders.

Keywords: ADHD, PPI, P50 suppression, gating.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a serious mental disorder with an early onset and a persistent pattern of severely impaired attention and concentration, hyperactive and impulsive behaviour, emotional instability, restlessness, and disorganized behaviour (American Psychiatric Association, 2000). Although long perceived as a disorder in children, ADHD symptoms persist in adulthood (Barkley, 1990; Mannuzza, Klein, & Addalli, 1991; Weiss, Hechtman, Milroy, & Perlman, 1985) including cases with partial remission (Faraone, Biederman, & Mick, 2006). Deficient information processing and impaired perceptual capacity in ADHD patients are thought to result in sensory overload which in turn may underlie ADHD symptoms, e.g. the inability to regulate attention volitionally and to constrain distraction (Armstrong, Hayes, & Martin, 2001; Spencer, Biederman, & Mick, 2007). A failure to inhibit irrelevant sensory stimuli is consistent with the tendency of individuals suffering from ADHD to switch prematurely from relevant to irrelevant cognitive processes (Armstrong et al., 2001). The inability to filter out extraneous stimuli and to attend to salient features of the environment implicates a deficit in gating, which is characterized by a general reduction of the ability to gate intrusive sensory, motor, and/or cognitive information (Geyer et al., 1987; Braff & Geyer, 1990).

Two distinct operational measures designed to assess gating or central inhibition are prepulse inhibition (PPI) of the acoustic startle response, considered to be a form of sensorimotor gating, and suppression of the P50 auditory event-related potential (AEP) in a condition-test paradigm (P50 suppression), considered to be a form of sensory gating. PPI refers to the attenuation of the reflexive startle reaction elicited by an intense startling stimulus when its presentation is preceded shortly (30 to 300 ms) by a weak prepulse stimulus (Graham, 1975; Hoffman & Ison, 1980). P50 suppression refers to the decrement of the P50 AEP to the second (S_2) vs the first (S_1) of two identical auditory stimuli presented in succession at an interstimulus interval of approximately 500 ms. It has been shown repeatedly that PPI and/or P50 suppression are impaired in various psychiatric disorders that show similar or overlapping cognitive impairments and/or deficient attention modulation such as found in schizophrenia disorders (Adler et al., 1982; Adler et al., 2004; Baker et al., 1987; Cadenhead, 2002; Light & Braff, 1999), psychotic mania (Perry, Minassian, Feifel, & Braff, 2001), obsessive compulsive disorder (Hoenig, Hochrein, Quednow, Maier, & Wagner, 2005; Swerdlow, Benbow, Zisook, Geyer, & Braff, 1993), Huntington's disease (Valls-Sole, Munoz, & Valldeoriola, 2004; Swerdlow et al., 2001; Swerdlow et al., 1995), Tourette's syndrome (Castellanos et al., 1996; Swerdlow, Zinner, Hartston, Filion, & Magulac, 1994a; Swerdlow, Zinner, Hartston, Filion, &

Magulac, 1994b), autism (Perry, Minassian, Lopez, Maron, & Lincoln, 2007), and posttraumatic stress disorder (PTSD) (Holstein, Vollenweider, Jäncke, Schopper, & Csomor, 2010). In contrast to these findings, it is not yet established whether gating functions, as measured by means of PPI and P50 suppression, are impaired in ADHD patients. Patients suffering from ADHD report being flooded with sensory input and exhibit deficits in cognitive domains comparable to those found in the above-mentioned disorders (Biederman, 2005; Faraone et al., 2000;). The few studies investigating sensorimotor gating functions in ADHD patients revealed no differences between patients and healthy controls (Feifel, Minassian, & Perry, 2009; Hanlon, Karayanidis, & Schall, 2008), except when attention is directed to the prepulse stimuli (Hawk et al., 2003) or when the ADHD is accompanied by a tic disorder or primary nocturnal enuresis (Castellanos et al., 1996; Ornitz, Hanna, & de Traversay, 1992; Ornitz et al., 1999). The only study that explored P50 suppression in ADHD patients compared to healthy controls reported no significant differences (Olincy et al., 2000). Until now, no study has investigated PPI and P50 in the same cohort of patients suffering from ADHD.

Cognitive impairment is a common finding in the population of ADHD patients (Dinn, Robbins, & Harris, 2001; Murphy, 2002; Ossmann & Mulligan, 2003). McLean et al. (2004)) showed that adult ADHD was associated with deficits in working memory, planning, and spatial working memory (SWM), reminiscent of childhood ADHD (Solanto, 1998). While impaired cognition and deficient gating seem to be at least partly associated in disorders such as schizophrenia (Geyer, 2006; Ludewig, Geyer, & Vollenweider, 2003; Scholes & Martin-Iverson, 2009), studies investigating both forms of gating and cognitive performances as well as their inter-relationships are still lacking in ADHD patients.

The primary aim of the present study was to investigate two different forms of gating and their potential relationships to psychopathology. To this end, sensory and sensorimotor gating as indexed by P50 suppression and PPI, cognitive performance as measured by a subset of CANTAB tasks, and psychopathological measures were assessed within the same patients suffering from ADHD in comparison to healthy control subjects. The hypotheses being tested were that ADHD patients would exhibit reduced P50 suppression, reduced PPI, and deficits in cognitive performance.

Methods and Materials

The study was approved by the ethics committee of Zurich canton and all subjects gave their informed written consent after being given complete explanations about the protocol and the purpose of the study. All subjects were instructed to abstain from drinking alcohol for at least

24 hours before each test session, not to drink any caffeine-containing beverages on the day of testing, and to keep their usual smoking habits (smoking was not allowed for 30 minutes prior to the test session).

Participants and Experimental Design

Twenty-six patients suffering from ADHD (see Table 1), diagnosed by a clinical Interview and a structured interview (Wender-Reimher Interview), as well as by self reports (German version of the Wender Utah Rating Scale, short version [WURS-K], ADHD-Self-Rating Scale German version [ADHS-SB]) (Retz-Junginger et al., 2003), were recruited through the in- and out-patient services of the Psychiatric University Hospital Zurich. Twenty-three patients with the diagnosis of combined type and 3 patients with the inattentive type were included into the study, all meeting the DSM-IV criteria for ADHD. Furthermore, 26 age- and gender-matched healthy volunteers were recruited by local advertisement and served as a comparison group (see Table 1). According to the Structured Clinical Interview for DSM-IV (SCID I; Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997), all participants were without a history or current presence of major psychotic and neurological disorders, and denied the use of illicit drugs. Moreover, all healthy subjects were without a history or current presence of psychiatric disorder. All participants completed the Hopkins Symptom Checklist (SCL-90-R; Derogatis, 1977), the NEO-Five Factor Inventory (NEO-FFI; Costa & McCrae, 1992), the Beck Depression Inventory (BDI; Beck & Steer, 1987), and the State-Trait-Anxiety-Inventory (STAI; Spielberger, Gorsuch, & Lusheme, 1970). Healthy control subjects were free of any medication for at least 3 weeks before the experiment and ADHD patients had taken their last stimulant medication at least 5 half-lives before starting the test session. On the experimental day, subjects completed the psychometric questionnaires and hearing was evaluated using a pure tone (tone frequencies: 500, 1000, 2000, 4000, 6000 Hz) audiometer (Earscan 3, Micro Audiometrics Corp., NC, USA). No subject was excluded due to hearing difficulties (hearing threshold > 30 dB_{HL}). Subjects first underwent the P50 suppression test session and then the PPI assessment 5 min later. After detaching all electrodes used in the electrophysiological recordings, subjects underwent neuropsychological testing using a subset of CANTAB tests.

PPI and P50 Suppression Session Definitions

The PPI test session was composed of a mixture of pulse-alone trials, prepulse-pulse trials, and trials in which no discrete stimulus was presented (‘no-stimulus’ or ‘NS trials’). All stimuli (background noise, pulses, and prepulses) consisted of broadband white noise. The intensity of

the continuous background noise was set at 70 dB_A. Pulse stimulus intensity was set in 2 different conditions at 110 and 115 dB_A and the prepulse stimulus intensity at 86 dB_A. The stimulus duration was 40 ms for pulse stimuli and 20 ms for prepulse stimuli. Rise and fall times of the stimuli were less than 1 ms. The 4 stimulus onset asynchronies (SOA) between the prepulse and pulse stimuli on prepulse-pulse trials were 30, 60, 120, and 2000 ms (SOA 30, SOA 60, SOA 120, and SOA 2000). The session began with a 2 min period of acclimatization to the background noise, followed by the presentations of 87 discrete trials according to a variable inter-trial interval ranging from 7 to 13 s (mean: 9.9 s). The 1st block consisted of 6 consecutive pulse-alone trials (3 of each intensity), although the 1st trial at each intensity was not used in analyses. The last block consisted of 4 consecutive pulse-alone trials (2 of each intensity). The middle block consisted of 77 trials, i.e. 7 trials of each of the 11 conditions (pulse-alone, prepulse-pulse combinations, and NS trial). The sequence of presentation was pseudo-randomized and was the same for all subjects. The PPI test session lasted approximately 18 min.

The P50 suppression test session was composed of 80 pairs of auditory clicks with a 500 ms inter-click interval presented fix every 10 s (mean). Stimuli consisted of 85 dB_A white noise with a duration of 1 ms. The P50 suppression session lasted for approximately 15 min.

Apparatus, Data Recording and Data Processing

For detailed information about apparatus and the EMG and EEG data processing see Csomor et al. (2008).

Assessed Parameters

For the PPI paradigm, the following startle measures were examined: (1) Pulse-alone: The mean *startle* reactivity elicited by the pulse-alone stimulus in each of the three blocks was calculated for each subject and both intensities. (2) PPI: *Percentage PPI* (%PPI) was calculated for each SOA by the formula: $[(1-(\text{amplitude}_{\text{prepulse-pulse}}) / (\text{amplitude}_{\text{pulse-alone(block2)}})] \times 100\%$. (3) *Percentage Habituation*: The reduction of the startle amplitudes between the first and last block was calculated according to the formula: $[1-(\text{amplitude}_{\text{pulse-alone(block3)}}) / (\text{amplitude}_{\text{pulse-alone(block1)}})] \times 100\%$.

For the P50 suppression paradigm, the following ERP measures were examined: (1) *P50 amplitudes* evoked by S_1 and S_2. (2) P50 suppression: *P50 differences* was calculated by the formula $[S_1-S_2]$, *P50 ratio* was calculated by the formula $[S_2/(S_1+S_2)]$ and *percentage P50*

suppression was calculated by the formula: [1 - (amplitude$_{s2}$) / (amplitude$_{s1}$)] x 100%. (3) *Latency* of P50 amplitude$_{s1}$ and amplitude$_{s2}$.

Three tests of the CANTAB were administered using an IBM-compatible PC with a touch-screen monitor (Elo IntelliTouch®, Tyco Electronics, PA, USA): (1) *Rapid visual information processing* (RVP), (2) *Spatial Working Memory task* (SWMT), and (3) *Stockings of Cambridge* (SOC). For a more detailed description of the used tasks see (Csomor et al., 2008).

Statistical Analysis

All statistical analyses were conducted using the statistical software Statistica 7 for Windows (Statsoft Inc., OK, USA). The Shapiro-Wilk test was used to identify skewed distributions, with the alpha level set at $p< 0.05$.

The distribution of the PPI startle amplitudes in patients and controls was positively skewed in most of the blocks. In the P50 suppression paradigm distribution, most of the S_1 and S_2 amplitudes were positively skewed. After ln-transformation, startle amplitudes did not deviate significantly from normality. Similarly, square-root-transformation (sqrt-transformation) of P50 amplitudes elicited by S_1 and S_2 resulted in a normal distribution. While statistical comparisons of pulse-alone elicited startle reactivity was based on ln-transformed startle data and P50 amplitudes were based on sqrt-transformed P50 amplitudes, the calculations of %PPI and %P50 suppression were based on non-transformed data. Furthermore, data of P50 latencies were based on non-transformed data.

Startle amplitudes were analyzed using repeated measures analysis of variance (ANOVA) block (1 to 3) and intensity (110 vs. 115 dB_A) as within-subject factors and group (patients vs. controls) as between-subject factors. Similarly, %PPI values for the inhibitory SOAs (30, 60, 120 ms) were subjected to a 3 × 2 × 2 (SOA × intensity × group) repeated measures ANOVA. Prepulse facilitation (PPF) (SOA: 2000 ms) and %habituation were analyzed separately by one-way ANOVAs.

P50 amplitude and latency were analyzed by separate repeated measures ANOVAs with stimulus number (S_1 and S_2) as a within-subject factor and group (patients vs. controls) as a between-subject factor. The %P50 suppression data were analyzed by one-way ANOVA.

Separate two-way ANOVAs with group (separately for P50 and PPI patients and controls) and treatment were used to examine the group effect on the performance of RVP CANTAB tasks. For the SOC and SWM tasks, the additional factor “difficulty” was introduced.

Similarly, differences in SCL-90 global factor and sub factor, BDI, STAI and NEO-FFI scores between the 2 groups were assessed by separate repeated measures ANOVAs.

For statistical tests, the significance level was set to $p < 0.05$. Post-hoc pair-wise comparisons were conducted using Fisher's Least Significant Difference (Fisher LSD). In the case of significant effects, the effect size expressed as partial eta-squared (η_p^2) was calculated. For the potential commonalities between PPI and P50 suppression and for the relationships between CANTAB scores and gating measures, Pearson correlations were calculated. Due to the high number of correlations (42) examined, the Pearson correlations alpha was set to $p < 0.001$.

Results

Psychometric data

ADHD Patients and controls did not differ in age, IQ, or alcohol or nicotine consumption. Patients exhibited significantly higher scores of personality factor neuroticism, while showing significant lower scores of agreeableness and conscientiousness in the NEO-FFI. Patients also scored significantly higher in BDI, STAI, and all SCL-90 global indices and subscale scores (Table 1).

Table 1: Demographic characteristics and psychometric data

	Patients (n=26)		Controls (n=23)		main effect of group		
Psychometric	Mean	SE	Mean	SE	F	p	η_p^2
Gender							
Male	18		18				
Female	8		8				
Age	32.58	2.10	32.58	2.10	0.01	1	
IQ*	108.28	3.00	113.92	3.28	1.61	0.21	
Nicotine (cigarettes/day)	27.20	9.09	18.96	6.17	0.57	0.45	
Alcohol (dl/week)	4.00	1.23	3.25	0.62	0.3	0.58	
NEO-Five Factor Inventory (NEO-FFI)							
Neuroticism	3.58	0.22	1.62	0.12	**64.79**	**< 0.001**	**0.57**
Extraversion	3.41	0.16	3.78	0.12	3.57	0.065	0.07
Openness to experience	3.83	0.19	3.85	0.15	0.01	0.94	
Agreeablness	3.28	0.16	4.26	0.10	**27.16**	**< 0.001**	**0.37**
Conscientiousness	2.96	0.14	4.40	0.12	**65.3**	**< 0.001**	**0.57**
Beck Depression Inventory (BDI)	13.25	2.00	1.27	0.36	**37.39**	**< 0.001**	**0.44**
State-Trait-Anxiety-Inventory							
State Score	49.60	2.22	29.62	1.09	**66.97**	**< 0.001**	**0.58**
Trait Score	49.08	2.18	28.88	0.98	**73.31**	**< 0.001**	**0.60**
SCL-90 Global Indices:							
Global Severity Index (GSI)	1.24	0.13	0.16	0.02	66.44	**< 0.001**	**0.58**
Positive Symptom Total (PST)	51.20	3.88	11.96	1.61	89.60	**< 0.001**	0.65
Positive Symptom Distress Index (PSDI)	2.09	0.10	1.17	0.04	71.95	**< 0.001**	0.60
SCL-90 Symptom Subscales:							
Somatization	0.80	0.14	0.19	0.04	17.72	**< 0.001**	0.27
Obsessive-Compulsive	1.79	0.17	0.23	0.05	80.76	**< 0.001**	0.62
Interpersonal Sensitivity	1.45	0.17	0.13	0.03	63.82	**< 0.001**	**0.57**
Depression	1.56	0.18	0.21	0.04	52.71	**< 0.001**	**0.52**
Anxiety	1.32	0.15	0.13	0.03	61.38	**< 0.001**	**0.56**
Hostility	1.49	0.18	0.15	0.03	57.88	**< 0.001**	0.54
Phobic Anxiety	0.58	0.12	0.04	0.02	19.48	**< 0.001**	0.29
Paranoid Ideation	1.31	0.19	0.15	0.05	34.73	**< 0.001**	0.41
Psychoticism	0.83	0.14	0.05	0.02	33.00	**< 0.001**	0.40

* measured by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl 1999)

Prepulse Inhibition Paradigm

Data of 6 patients and 6 control subjects were rejected as no distinct startle reaction was elicited by pulse-alone stimuli (non-responders, mean startle amplitude < 10 μV in the presentation block relevant for %PPI calculation). As summarized in Table 2, patients and controls did not differ in startle amplitude, %PPI, or %habituation. As expected, startle amplitude diminished in both intensity conditions over the three blocks of the testing session. Startle amplitude was higher in the 115 dB_A condition compared to the 110 dB_A condition and %habituation was higher at 110 dB_A intensity. All results are summarized in Table 2. Moreover, because in the 115 dB_A condition, PPI only data from 5 patient and 4 control subjects had to be excluded due to the absence of a distinct startle reactions, additional analysis of startle and PPI was performed separately for pulse-intensity conditions of 110 and 115 dB_A, revealing no group differences. Additional analysis of %PPI adding the factor "gender" revealed that males (independent of group) showed a higher %PPI [$F(1,36) = 11.21$, $p < 0.01$, $\eta_p^2 = 0.24$]. Moreover, additional analysis of %PPI adding the factor "medication" (medicated the days before the test session vs. never medicated) within the patients group was performed, revealing no significant main effects, but significant interactions of medication x intensity [$F(1,18) = 16.95$, $p < 0.001$, $\eta_p^2 = 0.49$], intensity x SOA [$F(2,36) = 7.83$, $p < 0.05$, $\eta_p^2 = 0.30$], and medication x intensity x SOA [$F(2,36) = 4.02$, $p < 0.05$, $\eta_p^2 = 0.18$], indicating a lower %PPI in medicated patients at the 115 dB_A at all SOA conditions. Post hoc comparisons revealed that %PPI of medicated vs. un-medicated patients did not differ significantly at the same intensity and SOA levels.

Table 2: PPI characteristics of ADHD patients and controls

	Patients (110 dBA: n=20) (115 dBA: n=21)		Controls (110 dBA: n=20) (115 dBA: n=22)		main effect of group			main effect of intesity			group x intensity interaction		
Electrophysiology	Mean	SE	Mean	SE	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
PPI paradigm													
Startle amplitude LN transformed (µV)[a]					0.17	0.68		**73.70**	**< 0.001**	**0.670**	0.01	0.91	
110 dBA[b]					0.10	0.75							
Block 1	4.72	0.14	4.94	0.14									
Block 2	3.69	0.16	3.75	0.21									
Block 3	3.33	0.21	3.26	0.23									
115 dBA[c]					0.02	0.88							
Block 1	4.92	0.10	4.87	0.16									
Block 2	4.39	0.15	4.36	0.17									
Block 3	4.07	0.17	4.04	0.23									
Non-stimulus	1.38	0.12	1.13	0.10	2.65	0.11							
Habituation					0.01	0.98		**18.85**	**< 0.001**	**0.340**	1.21	0.28	
110 dBA (%)	66.90	6.19	73.22	5.53	0.58	0.45							
115 dBA (%)	49.71	5.71	38.80	10.02	0.87	0.36							
Inhibition (%)[d]					0.69	0.41		0.29	0.59		1.2	0.28	
110 dBA[e]					0.04	0.84							
SOA 30 ms	10.34	10.88	16.86	9.58									
SOA 60 ms	66.11	5.16	59.68	8.04									
SOA 120 ms	75.36	3.33	70.45	4.98									
SOA 2000 ms	-0.35	7.03	-20.86	12.81	1.97	0.17							
115 dBA[f]					0.54	0.47							
SOA 30 ms	30.31	10.58	24.94	6.43									
SOA 60 ms	64.13	5.57	56.57	7.27									
SOA 120 ms	61.48	6.11	56.74	6.90									
SOA 2000 ms	-6.44	9.29	-18.43	12.13	0.61	0.44							

[a] Repeated measures ANOVA including factor "block". Significant main effect of block [F(2,72)=85.58, p<0.001] and intensity x block interaction [F(2,72)=25.85, p<0.001].
[b] Repeated measures ANOVA including factor "block". Significant main effect of block [F(2,72)=23.86, p<0.001].
[c] Repeated measures ANOVA including factor "block". Significant main effect of block [F(2,78)=37.68, p<0.001].
[d] Repeated measures ANOVA including factor "SOA". Significant main effect of SOA [F(2,76)=49.70, p<0.001] and intensity x SOA interaction [F(2,76)=12.93, p<0.001].
[e] Repeated measures ANOVA including factor "SOA". Significant main effect of SOA [F(2,76)=51.07, p<0.001].
[f] Repeated measures ANOVA including factor "SOA". Significant main effect of SOA [F(2,82)=21.76, p<0.001].

P50 Suppression Paradigm

P50 data of 3 patients and 3 control subjects were rejected because no distinct P50 component elicited by S1 could have been identified. As shown in Table 3, patients exhibited significantly less P50 suppression (%P50 as well as higher P50 ratio and lower P50 difference scores) compared to the control group. Analysis of P50 amplitudes revealed a significant main effect of 'stimulus type', confirming the occurrence of P50 suppression. Moreover, the interaction between the factors 'stimulus type' and 'group' attained significance. Post-hoc testing revealed that the amplitudes elicited by S_1 and S_2 did not differ significantly between patients and controls. No significant effects were detected in the analysis of P50 latencies (Table 3). Additional analysis of %P50 suppression adding the factors "gender" and separate analysis of the factor "medication" within the patient group revealed no significant main effects or interactions.

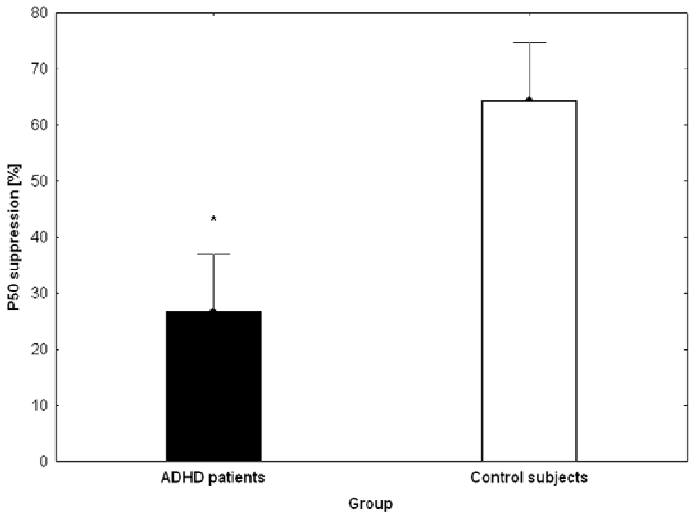

Figure 1. Percentage P50 Suppression of the ADHD patients and healthy control subjects. Error bars refer to ±SE.

Table 3: P50 suppression characteristics of ADHD patients and controls

	Patients (n=23)		Controls (n=23)		main effect of group			main effect stimulus number			group x stimulus number interaction		
Electrophysiology	Mean	SE	Mean	SE	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
P50 suppression paradigm													
Amplitudes SRQ transformed (µV)					0.07	0.79		**51.03**	**< 0.001**	**0.54**	**7.57**	**< 0.01**	**0.15**
Conditioning stimulus (s1)	1.01	0.09	1.15	0.07									
Test stimulus (s2)	0.75	0.08	0.56	0.08									
Latency (ms)					0.41	0.53		0.48	0.49		0.34	0.56	
Conditioning stimulus (s1)	57.83	1.27	59.78	1.14									
Test stimulus (s2)	59.78	2.32	59.95	1.41									
P50 Difference scores (S1-S2)	0.49	0.16	0.99	0.17	**4.47**	**< 0.05**	**0.09**						
P50 Suppression (ratio)	0.36	0.04	0.23	0.03	**6.15**	**< 0.05**	**0.12**						
P50 Suppression (%)	26.67	13.15	64.29	6.50	**6.58**	**< 0.05**	**0.13**						

Neuropsychological Testing

Patients and controls differed in several cognitive domains. Patients performed significantly worse in the RVP sustained attention task, as indicated by a lower detection sensitivity (*A'*) score and by a lower number of *total hits*. Patients also showed a significant higher *total error* and a worse *strategy score* and made more *between errors* in the spatial working memory (SWM) task. Moreover, analysis of the SWM *between errors* revealed a significant interaction with the factors group and difficulty. Post-hoc testing confirmed that patients performed significantly worse at difficulty level 2 ($p < 0.05$) and level 3 ($p < 0.001$), but not at level 1. Furthermore, in the SOC planning task, patients needed significantly more moves and solved fewer problems in minimum moves than healthy controls. All results are summarized in Table 4.

Table 4: Neuropsychological characteristics of ADHD patients and controls

	Patients (n=26)		Controls (n=23)		main effect of group			main effect of difficulty			group x difficulty interaction		
CANTAB tasks	Mean	SE	Mean	SE	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
RVP[1]													
A'	0.87	0.01	0.92	0.01	**13.15**	**<0.001**	**0.21**						
B'	0.94	0.01	0.96	0.01	0.78	0.38							
Latency (ms)	489.57	22.03	442.65	23.75	2.09	0.15							
Total hits	12.81	1.06	18.46	0.95	**15.76**	**<0.001**	**0.24**						
SWM[2]													
Between errors[a]					**11.59**	**<0.01**	**0.19**	**47.56**	**<0.001**	**0.49**	**5.38**	**<0.01**	**0.10**
Difficulty level 1	1.08	0.27	0.85	0.37									
Difficulty level 2	7.12	1.31	1.27	0.49									
Difficulty level 3	16.58	2.49	8.54	1.85									
Strategy	31.23	1.28	27.54	1.21	**4.40**	**<0.05**	**0.09**						
Total errors	25.50	3.53	10.88	2.32	**11.95**	**<0.01**	**0.19**						
SOC[3]													
Initial thinking time (ms)[b]					0.74	0.39		**53.15**	**<0.001**	**0.52**	1.23	0.30	
Difficulty level 1	1793.54	176.61	1969.37	141.99									
Difficulty level 2	6175.17	774.28	5073.81	518.54									
Difficulty level 3	8888.93	1191.15	10420.22	1115.10									
Difficulty level 4	14446.68	2353.10	17665.78	2029.25									
Mean moves[c]					**6.20**	**<0.05**	**0.11**	**337.71**	**<0.001**	**0.87**	2.16	0.10	
Difficulty level 1	2.04	0.04	2.00	0.00									
Difficulty level 2	3.31	0.13	3.12	0.04									
Difficulty level 3	5.36	0.18	4.97	0.20									
Difficulty level 4	6.44	0.24	5.72	0.21									
Subsequent thinking time (ms)[d]					1.96	0.17		**25.16**	**<0.001**	**0.34**	0.96	0.41	
Difficulty level 1	76.63	29.61	119.52	37.59									
Difficulty level 2	307.71	138.08	188.49	53.81									
Difficulty level 3	1425.86	282.01	1077.92	241.65									
Difficulty level 4	888.66	187.28	498.15	125.87									
Problems solved in min. moves	8.62	0.37	9.81	0.33	**5.70**	**<0.05**	**0.10**						

[1]Rapid visual information processing, [2]Spatial working memory, [3]Stockings of Cambridge

Moreover, additional analysis of the factor "medication" revealed a significant interaction between the factors medication x difficulty [$F(3,72) = 3.03$, $p < 0.05$, $\eta_p^2 = 0.11$] on the *subsequent thinking time* score of the SOC task. Post hoc tests showed that medicated patients had a significantly higher *subsequent thinking time* at difficulty level 3 than un-medicated patients. For all other CANTAB tasks, no significant main effects or interactions for the factor "medication" were found.

Pearson correlation analyses conducted between neurophysiological measures (%P50 suppression, %PPI, startle, and habituation), psychometric ratings (NEO-FFI, SCL-90, STAI, and BDI scores), and CANTAB task performances did not reach statistical significance.

Specifically, and in contrast to previous findings (Csomor et al., 2008), the correlations between %PPI and SWM strategy score ($110dB_A$: $r_{SOA30} = -0.12$; $r_{SOA60} = -0.10$; $r_{SOA120} = -0.17$; $115dB_A$: $r_{SOA30} = -0.17$; $r_{SOA60} = -0.20$; $r_{SOA120} = -0.15$) were low and not significant. Also the correlations between PPI and P50 suppression were not significant ($110dB_A$: $r_{SOA30} = -0.01$; $r_{SOA60} = 0.06$; $r_{SOA120} = 0.07$; $115dB_A$: $r_{SOA30} = -0.03$; $r_{SOA60} = -0.13$; $r_{SOA120} = -0.13$), supporting the notion that these measures are linked to different/independent gating processes.

DISCUSSION

To our knowledge, this is the first study investigating PPI, P50 suppression, and cognitive performances within the same ADHD patient group. The current results indicate that ADHD patients showed a significant disruption in P50 suppression but not in PPI and were impaired in several cognitive domains compared to normal controls. Patients also differed in several personality factors and exhibited substantial psychopathological symptoms.

PPI

The present results revealed that ADHD patients showed similar sensorimotor gating and startle reactivity as do healthy controls. These findings are in agreement with recent published studies investigating PPI in adults suffering from ADHD (Feifel et al., 2009; Hanlon et al., 2008). However, some small studies have suggested that ADHD patients with a comorbid tic disorder or primary nocturnal enuresis have reduced PPI (Castellanos et al., 1996; Ornitz et al., 1992; Ornitz et al., 1999). Therefore, the comorbid disorder seems to be an important contributor to the diminished PPI observed in these ADHD patients. Although dopamine is believed to play an important role in the pathophysiology underlying ADHD symptomatology (Biederman & Faraone, 2005; Staller & Faraone, 2007) and dopaminergic interventions influence PPI (Braff, Geyer, & Swerdlow, 2001), reduced PPI seems not to be a trait marker for ADHD.

Moreover, the absence of a PPI deficit in the present study and in the above-cited literature could be due to our use of a passive PPI paradigm since other findings have been reported for active listening paradigms. For example, Hawk, Jr., Yartz, Pelham, Jr., and Lock (2003) reported no PPI differences in boys (age 10-12 years) suffering from ADHD when they were instructed to ignore the prepulse stimuli, although they showed diminished sensorimotor gating when instructed to attend to the prepulse stimuli. Moreover, treatment with methylphenidate enhanced PPI only during attended, but not during ignored stimuli in children suffering from ADHD (Ashare et al., 2010). Adult ADHD patients did not differ from healthy controls in either attended or ignored conditions, nor did stimulant treatment affect their PPI (Hanlon et al., 2008). Therefore, attention deficits in adult ADHD cannot be directly associated or related to an impaired PPI. As reviewed above, although PPI deficits are found in schizophrenia spectrum and some other psychiatric disorders (Braff et al., 2001), investigations of other neuropsychiatric illnesses such as PTSD (Braff et al., 2001; Holstein et al., 2010), anxiety disorders, depression (Ludewig & Ludewig, 2003; Quednow et al., 2006; Quednow, 2008), ADHD revealed no diminished PPI. While no standardized parameter assessment for

sensorimotor gating has been established in schizophrenia research, this has been discussed for other disorders (Braff et al., 2001; Holstein et al., 2010). However, the parameters of the present study are very comparable to those used in other studies investigating PPI in adult ADHD (115 dB pulse stimulation, at least SOA 30, 60, 120 ms background white noise) (Feifel et al., 2009; Hanlon et al., 2008) supporting the conclusion that ADHD patients and control subjects do not differ in PPI.

Even though none of the ADHD patients were medicated on the day of the test session, some patients were taking stimulant medication (methylphenidate) the days before testing ($n_{medicated}$ = 7) and some were not ($n_{unmedicated}$ = 19). Furthermore, activation of dopamine receptors (with direct and indirect agonists) influences PPI (Braff et al., 2001), and there are considerations from animal studies that methylphenidate diminishes PPI in rodents (Drolet, Proulx, Pearson, Rochford, & Deschepper, 2002; Issy, Salum, & Del Bel, 2009). Even though we ensured that ADHD patients were without any medication for at least 5 half-lifes, one might argue that a medical therapy over several months and years has a long lasting influence on the dopamine system. Therefore, as reported in the results section, additional analysis of the factor treatment in the patient group indicated a lower PPI in medicated compared to non-medicated patients at an intensity level of 115 dB_A at all SOA conditions. Consequently, the absence of PPI differences between ADHD patients and controls in the present study underlines the absence of a diminished PPI in ADHD. Moreover, larger sample size studies with a longitudinal design investigating systematically the influence of stimulant medication on PPI in ADHD are necessary to investigate potential PPI differences in ADHD patients treated with stimulants compared to those who were not and/or never treated.

P50

Reduced sensory gating in the present group of ADHD patients was due to differences in the amplitudes elicited by S_2, rather than S_1, and therefore can be interpreted as an impairment in central inhibitory activity (Ghisolfi et al., 2004; White & Yee, 1997). The current finding of reduced sensory gating in ADHD stands in contrast to the only previous study investigating P50 suppression in ADHD (Olincy et al., 2000). Olincy et al. (2000) reported in their study that most un-medicated adults with ADHD showed a P50 suppression that was comparable to that seen in healthy subjects, although 25% of this sample did not suppress the response to the second stimulus. Although the rate of non-suppression in ADHD patients was higher than the 10% rate previously observed in normal subjects (Freedman et al., 1994), this finding was not significant. The authors suggested that this lack of significance may have been due to the small

sample size of their study (16 ADHD subjects) (Olincy et al., 2000). Our study was based on a larger sample size using a parameter setting comparable to other studies (Csomor et al., 2008; Holstein et al., 2010). Therefore, an explanation and potential confounding factor responsible for divergent results could be a different parameter setting in the Olincy study. They used a total number of 48 stimuli (compared to 80 of the present study) and a stimulus intensity of 70 dB_A (present study 85 dB_A), which might be not large enough to generate robust results. De Wilde, Bour, Dingemans, Koelman, and Linszen (2007) concluded that the optimal level of sound intensity seems to be between 85 and 90 dB_A. Moreover, they reported differences in P50 suppression according to the subject's position during electrophysiological recording (de Wilde et al., 2007). While in the present study subjects were sitting in an upright position, in the Olincy et al. (2000) study subjects were in a supine position. Thus, one or more of these differences in the testing conditions may partly account for the diverse finding leading to the conclusion, that it is imperative to establish firm experimental parameters enabling effective comparisons of results between laboratories.

P50 gating deficits are found in several other psychiatric disorders such as schizophrenia (Adler et al., 1982; Braff, Light, & Swerdlow, 2007; Light & Braff, 1999; Cadenhead, 2002; de Wilde et al., 2007), schizotypal personality disorder (Cadenhead, Light, Geyer, McDowell, & Braff, 2002), psychotic bipolar disorder (Hall et al., 2008; Schulze et al., 2007), PTSD (Holstein et al., 2010; Neylan et al., 1999; Skinner et al., 1999; Ghisolfi et al., 2004; Gillette et al., 1997), and Alzheimer dementia (Thomas et al., 2008). Consequently, P50 gating is not exclusively associated with a specific disorder. Moreover, impaired P50 suppression might be a general and common feature of several psychiatric disorders sharing deficits in attention functions.

The present low correlations between PPI and P50 suppression confirm again that P50 gating and PPI represent distinct forms of gating, as already reported for both humans and animals elsewhere (Braff et al., 2007; Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004; Holstein et al., 2010; Light & Braff, 2001; Oranje, Geyer, Bocker, Leon, & Verbaten, 2006; Schwarzkopf, Lamberti, & Smith, 1993). Moreover, the present findings supports the suggestion that PPI and P50 suppression represent different aspects of attention and inhibition (Braff et al., 2007).

Contrary to our recent findings in PTSD patients (Holstein et al., 2010), the present study revealed no significant correlations between gating measures and psychological self ratings. ADHD patients reported significantly more anxiety, depression, and general psychopathological symptoms and described themselves differently in personality factors

(neuroticism, agreeableness, and conscientiousness) than the control group, as reported previously (Retz et al., 2004; Rosler et al., 2004).

Cognitive Performance

As predicted, ADHD patients performed worse compared to healthy controls in cognitive measures of attention, spatial working memory, and executive functions (planning and strategy). The present results are in line with previous findings. Impaired sustained attention is a common and robust finding in ADHD (Calis, Grothe, & Elia, 1990; Gallagher & Blader, 2001; Johansen, Aase, Meyer, & Sagvolden, 2002; Rodriguez-Jimenez et al., 2006). Moreover, decreased working memory (e.g. SWM) (Barkley, 1997; Gallagher & Blader, 2001; Dowson et al., 2004; Levy, 2009; McLean et al., 2004; Rodriguez-Jimenez et al., 2006) and difficulties in executive functioning (Greene, Braet, Johnson, & Bellgrove, 2008; McLean et al., 2004; Mercugliano, 1999; Rodriguez-Jimenez et al., 2006; Seidman, Biederman, Weber, Hatch, & Faraone, 1998) are often reported. At a neurobiological level, due to the ameliorating effect of stimulant medications (e.g. dopamine agonists) in ADHD treatment, a dysfunction in the dopamine system may contribute to ADHD symptoms (Johansen et al., 2002). Furthermore, dopamine acts as a key neurotransmitter in the brain and seems to be a modulator of different aspects of cognitive brain functions (Nieoullon, 2002). Numerous studies have shown its regulatory role for motor and limbic functions, as well as on a behavioral level, giving rise to deficient sustained attention, hyperactivity, motor abnormalities, and impulsiveness (Johansen et al., 2002). These features are comparable observation of children suffering from ADHD (Kempton et al., 1999). While there was no better performance within the subgroup of patients, taking stimulant medication prior to the present study, there is evidence, that long-term taking of stimulant medications improves performances in visual-spatial working (it reduces errors but has no effect on strategy score) (Goldberg et al., 2005), recognition memory (Coghill, Rhodes, & Matthews, 2007), SWM (Turner, Blackwell, Dowson, McLean, & Sahakian, 2005), and sustained attention (Turner et al., 2005). Furthermore, it has been reported that a single acute dose had no improving effect (Rhodes, Coghill, & Matthews, 2006).

No relation was found between gating measures and cognitive performances. Contrary to recent findings with healthy volunteers (Bitsios, Giakoumaki, Theou, & Frangou, 2006; Csomor et al., 2008; Giakoumaki, Bitsios, & Frangou, 2006), where a relation between sensorimotor gating and cognitive performance was found, the present study revealed no significant and relatively low correlations between these measures.

Limitations

The findings of the present study and its interpretation include some limitations. A confounding not controlled factor in the present study was the menstrual cycle in female participants, which is known to affect PPI. Furthermore, the majority of ADHD patients participating in the present study were diagnosed with the combined type, limiting the conclusions made to the mentioned ADHD subtype. In addition, larger sample sizes are warranted to investigate potential gating differences between ADHD subtypes (inattentive, hyperactive/impulsive, combined type, not otherwise specified).

Conclusion

The absence of diminished PPI in adult ADHD patients seems to be a robust finding. Furthermore, P50 gating deficits are not specific to schizophrenia spectrum disorders. Thus, sensorimotor and sensory gating measures can be used as informative and independent neurophysiological markers for studies investigating neuropsychiatric disorders and may well constitute separable endophenotypes. Further research is needed, including double-blind randomized longitudinal studies measuring ADHD patients before and while treated with stimulant medication, to investigate long lasting influences of stimulant medication on PPI in ADHD, and to evaluate whether operational measures of sensory gating have the potential to serve as efficacy markers for therapeutic outcome.

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The effects of sertindole on sensory gating, sensorimotor gating, and cognition in healthy volunteers

Dominique H. Holstein, Philipp A. Csomor, Mark A. Geyer, Theo Huber, Nicole Brugger, Erich Studerus, and Franz X. Vollenweider

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Chapter 4 is based on a paper submitted for publication in the Journal of Psychopharmacology, and consists of original works that I have contributed and participated directly including the design of experiments, collection of data, statistical analysis, and the preparation of the final manuscript, with the additional contributions by Dr. Csomor, Prof. Geyer, Dr. Huber, Ms. Brugger, Mr. Studerus, and Prof. Vollenweider, who appear as co-authors in the published paper.

Abstract

Sensory gating, indexed by P50 suppression, and sensorimotor gating indexed by prepulse inhibition (PPI), are impaired in schizophrenia spectrum disorders. There is considerable evidence that schizophrenia patients treated with atypical antipsychotics exhibit relatively less gating deficits than do other patients with schizophrenia. Some recent studies have investigated the effect of antipsychotic medications on gating in healthy volunteers exhibiting low levels of gating, rather than in patients. Therefore, the current study investigated the influence of sertindole vs. placebo in two separate experimental sessions, on PPI, P50 suppression, and cognition in 30 male volunteers stratified for low and high baseline gating levels. Sertindole increased PPI and P50 suppression in healthy subjects exhibiting low baseline PPI and low baseline P50 suppression respectively, while sertindole attenuated gating in subjects exhibiting high baseline gating. Furthermore, subjects exhibiting low PPI chose worse strategy in a spatial working memory task. These findings suggest that mixed D_2 / 5-HT_2 receptor antagonists modulate PPI as well as P50 suppression in a way to enhance it in healthy subjects with low baseline gating. Furthermore, the results militate in favor of the concomitant assessment of PPI, P50 suppression, and cognitive measures while investigating the effect of antipsychotic medication in healthy subjects.

Keywords: Schizophrenia, PPI, P50 suppression, gating, antipsychotics, sertindole psychophysiology

Introduction

Gating, an essential feature of early information processing, reflects the ability to inhibit extraneous stimuli and to attend to salient features of the environment. Two measures used to operationalize gating are prepulse inhibition (PPI) of the acoustic startle response, considered a form of sensorimotor gating, and suppression of the P50 auditory event-related potential (AEP) in a condition-test paradigm (P50 suppression), reflecting sensory gating. PPI refers to the attenuation of the reflexive startle reaction elicited by an intense pulse stimulus when its presentation is preceded shortly (30 to 300 ms) by a weak prepulse stimulus (Graham, 1975; Hoffman & Ison, 1980). P50 suppression refers to the decrement of the P50 AEP to the second stimulus (S_2) vs the first stimulus (S_1) of two identical auditory stimuli presented in succession at an interstimulus interval of approximately 500 ms. It has been shown repeatedly that both PPI and P50 suppression are impaired in schizophrenia spectrum disorders (Adler et al., 1982; Adler et al., 2004; Baker et al., 1987; Cadenhead, 2002; Csomor et al., 2008a; Light & Braff, 1999; Perry, Minassian, Feifel, & Braff, 2001). Theoretically, deficient gating is associated with a general reduction of the ability to gate intrusive sensory, motor, and/or cognitive information (Braff & Geyer, 1990; Geyer et al., 1987).

There is considerable evidence suggesting that schizophrenia patients treated with atypical antipsychotic medications exhibit relatively less PPI and P50 suppression deficits than do other patients with schizophrenia (Adler et al., 2004; Vrim-Ucok, Keskin-Ergen, & Ucok, 2008). In order to bridge the gap between basic and clinical research, some recent studies have investigated the effect of antipsychotic medications on gating in healthy volunteers exhibiting low levels of gating, rather than in patients. In this connection it has been shown that clozapine, as well as quetiapine, increased PPI in healthy subjects exhibiting low levels of sensorimotor gating at baseline (Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006b; Vollenweider, Barro, Csomor, & Feldon, 2006). In contrast, the typical antipsychotic haloperidol does not have such a PPI-enhancing effect (Csomor et al., 2008a). The translational approach of examining pharmacological manipulations in healthy individuals exhibiting naturally low levels of gating has also been adopted in a study assessing P50 suppression. Our group has shown that haloperidol increases P50 suppression in subjects exhibiting low P50 gating while it attenuated P50 suppression in subjects with high P50 gating (Csomor et al., 2008a). Others (Knott, Millar, & Fisher, 2009) have used a similar approach to localize the sources of the P50 response. Such concepts based on a selected cohort of healthy volunteers exhibiting traits

similar as observed in patients (i.e., low gating) might be useful in translational medicine as part of the discovery-cycle in the search of novel compounds with antipsychotic properties.

The current study investigates the influence of the atypical antipsychotic sertindole, which acts as a potent antagonist at dopamine-D_2 receptors, serotonin-$5HT_{2A}$ receptors, and α1-adrenoceptors, on gating and cognition in healthy volunteers exhibiting either low or high baseline gating levels. Although no previous studies have investigated the effects of sertindole on PPI or P50 suppression in humans, there is evidence from experiments with rodents that sertindole has the potential to increase PPI (Depoortere, Perrault, & Sanger, 1997; Paabol Andersen & Pouzet, 2001).

Furthermore, we (Vollenweider et al., 2006) and others (Swerdlow et al., 2006b) have shown that antipsychotics such as clozapine and quetiapine, which have a preferential antagonistic activity at D_2- and $5HT_{2A}$-receptors, can enhance PPI in healthy subjects with low baseline gating capacity. Based on these findings and the fact that sertindole shares certain mechanism of action (dopamine-D_2 and serotonin-$5HT_{2A}$ antagonism) with clozapine and quetiapine (Hertel, 2006) we hypothesized that sertindole would improve sensory and sensory motor gating in healthy subjects exhibiting relatively low baseline levels of PPI or P50 suppression. In addition, the current investigation assessed the extent to which cognition is modulated by sertindole, and also potential differences in cognitive performance between the low and high gaters. Interestingly, performance in cognitive tasks relying on prefrontal cortical functioning appears to differ between subjects with low and high sensorimotor gating. It has been shown that strategy formation and planning are diminished in healthy volunteers with low levels of PPI (Bitsios, Giakoumaki, Theou, & Frangou, 2006; Csomor et al., 2008a; Giakoumaki, Bitsios, & Frangou, 2006). With a translational approach in mind, these impairments parallel the findings of cognitive deficits, especially measured by (pre)frontal tasks, in schizophrenia spectrum disorders (Badcock, Michiel, & Rock, 2005; Hutton et al., 1998; Manoach, 2003; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Weickert et al., 2000).

In sum, we hypothesized that a moderate but clinically relevant dose of sertindole would enhance PPI and P50 suppression in healthy volunteers exhibiting low baseline gating. Furthermore, we predicted a replication of previous findings of reduced cognitive ability in subjects with low sensorimotor gating. To this end, healthy male volunteers stratified for low and high baseline gating levels were given 12 mg (p.o.) sertindole and placebo in two separate experimental sessions, and PPI, P50 suppression, and cognition were assessed.

Methods and Materials

Subjects

Thirty healthy male volunteers were recruited by local advertisement. Due to the occurrence of gender differences in PPI (Swerdlow, Hartman, & Auerbach, 1996), only male subjects were included. The study was approved by the ethics committee of Zurich canton and Swissmedic. All subjects gave their informed written consent, were without a history of mental and neurological disorders, had no history of an axis I disorder amongst their first-degree relatives, were free of any medication, and denied the use of illicit drugs, which was confirmed by urine toxicology. To ascertain the subjects' mental status, all subjects were screened by the DIA-X diagnostic expert system (Wittchen & Pfister, 1997), a semi-structured psychiatric interview and the Hopkins Symptom Checklist (SCL-90-R; Derogatis, 1977). Furthermore, all of the volunteers underwent clinical examination that included electrocardiography and blood analysis. Hearing was evaluated in all subjects, using a pure tone (tone frequencies: 500, 1000, 2000, 4000, 6000 Hz) audiometer (Earscan 3, Micro Audiometrics Corp., NC, USA). None of the subjects was excluded due to hearing difficulties (hearing threshold > 30 dB_{HL}). All subjects were instructed to abstain from drinking alcohol for at least 24 hours before each test session, not to drink any caffeine-containing beverages on the day of testing, and to keep their usual smoking habits. Potential drug abuse was checked by urine toxicology. Smoking was not allowed for one hour prior to the recording session.

Experimental Design

In a double-blind, placebo-controlled within-subjects design, participants received orally 12 mg sertindole (4+4+4 mg given in 24 hours intervals) or placebo (0+0+0 given in 24 hours intervals) in two experimental blocks 14-21 days apart. Sertindole (Serdolect®) and placebo (lactose) was obtained from Lundbeck (Lundbeck AG, Glattbrugg, Switzerland). On each experimental day, 8 hours after the last drug administration (sertindole maximum plasma levels will be reached at about 8-10 hours after administration), subjects underwent the PPI assessment followed by a short break prior to the P50 suppression session. After detaching all electrodes used in the electrophysiological recordings, subjects underwent neuropsychological testing using a subset of CANTAB tests. After testing, subjects were monitored clinically until side effects were diminished.

PPI and P50 Suppression Session Definition

The PPI test session was composed of a mixture of pulse-alone trials, prepulse-pulse trials and trials in which no discrete stimulus other than the constant background noise was presented (denoted hereafter as 'no-stimulus' or 'NS trials'). All stimuli (background noise, pulses, and prepulses) used in the experiment consisted of broadband white noise. The intensity of the background noise was set at 70 dB_A. Pulse stimulus intensity was set at 115 dB_A and the prepulse stimulus intensity at 86 dB_A. The stimulus duration was 40 ms for pulse stimuli and 20 ms for prepulse stimuli. Rise and fall times of the stimuli were less than 1 ms. The 4 stimulus onset asynchronies (SOA) between the prepulse and pulse stimuli on prepulse-pulse trials were 30, 60, 120, and 2000 ms (SOA 30, SOA 60, SOA 120, and SOA 2000). The session began with a 2 min period of acclimatization to the background noise, followed by the presentations of 47 discrete trials according to a variable intertrial interval ranging from 7 to 13 s (mean: 9.9 s). The 1st block consisted of 3 consecutive pulse-alone trials whereas the first trial was discharged. The last block consisted of 2 consecutive pulse-alone trials. The middle block consisted of 42 trials, i.e. 7 trials of each of the 6 conditions (pulse-alone, prepulse-pulse combinations, and NS trial). The sequence of presentation was pseudo-randomized. The PPI test session lasted approximately 11 min.

The P50 suppression test session was composed of 80 pairs of auditory clicks with a 500 ms interclick interval presented every 10 s. Stimuli consisted of 85 dB_A white noise with a duration of 1 ms. The P50 suppression session lasted for approximately 15 min.

Aparatus, Data Recording and Data Processing

For detailed information about apparatus and data processing see Csomor et al. (2008a). In short: A sampling rate of 4096 Hz for the PPI paradigm, and 512 Hz for the P50 paradigm was used. For the PPI paradigm, EMG activity was band-pass filtered (30–500 Hz), downsampled to 1000 Hz, and then rectified. Segmentation was performed from 50 ms prior to the onset of the relevant stimulus (the prepulse in prepulse-pulse trials, respectively the pulse in pulse-alone trials), and lasted to 2300 ms after stimulus onset for the PPI trials, and to 450 ms for the startle trials. EMG data were smoothed (time constant: 5 ms), and every trial was scored separately using emgBLINK version 1.2 (CST, Switzerland). Baseline amplitude was calculated by the mean response amplitude of the first 50 ms before pulse-stimulus onset. Stimulus response amplitudes were assessed as peak response minus baseline value of the respective trial. Peak response was defined as the highest reaction in the time window between stimulus onset and 150 ms after stimulus onset. Response amplitudes on NS trials were scored as peak response

sampled between 51 and 201 ms minus baseline value of the respective trial. Every trial was examined for sign of corrupted EMG signal.

P50 suppression data were band-pass filtered (2–70 Hz, 50 Hz notch). Independent component analysis was used to remove artifacts due to eye movements and blinks, EEG data were re-referenced to the average and segmented from 500 ms before to 1000 ms after the first click. For P50 amplitude the artifact-free segments were band-pass filtered (10-40Hz) and then resegmented 100 ms before click onset to 400 ms after click onset separately for both stimulus conditions (S_1 and S_2) and then averaged. The P50 component of the AEP was identified as the most positive deflection 40–80 ms after stimulus presentation and scored as described by Nagamoto, Adler, Waldo, and Freedman (1989). The P50 amplitude was scored as the absolute difference between the P50 peak and the preceding negative trough. Only data from the Cz location were analyzed where the maximum activity for the P50 AEP was expected (Clementz, Geyer, & Braff, 1998).

Assessed Parameters

For the PPI paradigm, the following startle measures were examined: (1) Pulse-alone: The mean *startle* reactivity elicited by the pulse-alone stimulus in each of the three pulse blocks was calculated for each subject. (2) PPI: *Percentage PPI* (%PPI) was calculated for each SOA by the formula: $[(1-(\text{amplitude}_{\text{prepulse-pulse}}) / (\text{amplitude}_{\text{pulse-alone(block2)}})] \times 100\%$. (3) *Percentage Habituation*: The reduction of the startle amplitudes between the first and last blocks was calculated according to the formula: $[1-(\text{amplitude}_{\text{pulse-alone(block3)}}) / (\text{amplitude}_{\text{pulse-alone(block1)}})] \times 100\%$.

For the P50 suppression, paradigm the following ERP measures were examined: (1) *P50 amplitudes* evoked by S_1 and S_2. (2) P50 suppression: *Percentage P50 suppression* was calculated by the formula: $[1-(\text{amplitude}_{s2})/(\text{amplitude}_{s1})] \times 100\%$. (3) *Latency* of P50 amplitude_{s1} and amplitude_{s2}.

As summarized briefly below, 3 tests of the CANTAB were administered using an IBM-compatible PC with a touch-screen monitor (Elo IntelliTouch®, Tyco Electronics, PA, USA): (1) *Motor screening* (MOT): All subjects were introduced to the touch-screen procedure by completing a simple motor screening task consisting of touching the center point of flashing crosses on the screen as soon as possible after its presentation. (2) *Rapid visual information processing* (RVP): This task is a visual continuous performance task using predefined sequences of three digits presented at a rate of 100 per minute so as to assess sustained attention over a period of 4 minutes. RVP performance was assessed by total correct responses

to target sequences (total hits), the sensitivity to detect target sequences (A'), the signal detection measure of the strength of trace required to elicit a response (B'), and the mean latency to target sequences. (3) *Spatial Working Memory* (SWM): This is a test of spatial working memory and strategy performance. The subject had to find a blue 'token' in each displayed box, while not returning to boxes in which a blue token had already been found. Performance was indexed by a strategy score, which represents the number of times the subject begins a new search with the same box. A high score represents poor use of this strategy and a low score equates to effective use. Furthermore, the total number of errors and between errors (searching a token in a box where one had already been found) was assessed.

Statistical Analysis

All statistical analyses were conducted using the statistical software Statistica 7 for Windows (Statsoft Inc., OK, USA).

The distribution of the startle amplitudes in patients and controls was positively skewed in most of the blocks. In the P50 suppression paradigm distribution, most of the S_1 and S_2 amplitudes were positively skewed. After ln-transformation, startle amplitudes did not deviate significantly from normality. Similarly, square-root-transformation (sqrt-transformation) of P50 amplitudes elicited by S_1 and S_2 resulted in a normal distribution. While statistical comparisons of pulse-alone elicited startle reactivity were based on ln-transformed startle data and P50 amplitudes were based on sqrt-transformed P50 amplitudes, the calculation %PPI and %P50 suppression were based on non-transformed data. Furthermore, data of P50 latencies were based on non-transformed data.

Startle and PPI data from 8 subjects were not included in the final analysis (due to a startle amplitude of < 10 μV) the sample to 22 valid subjects. Startle amplitudes were analyzed using repeated measures analysis of variance (ANOVA) block (1 to 3) and treatment (placebo vs. sertindole) as within-subject factors and group (low vs. high) as between-subject factors. Similarly, %PPI values for the inhibitory SOAs (30, 60, 120 ms) were subjected to a 3 × 2 × 2 (SOA × treatment × group) repeated measures ANOVA. Analyses of prepulse facilitation (PPF) (SOA: 2000 ms), NS stimulus condition, and %habituation were done separately using one way ANOVAs.

P50 suppression data of 5 subjects had to be excluded because no distinct P50 component could be identified, reducing the sample to 25 valid subjects. P50 amplitude and latency were analyzed by separate repeated measures ANOVAs with stimulus number (S_1 and S_2) and treatment (placebo vs. sertindole) as within-subject factors and group (low vs. high) as

between-subject factors. The %P50 suppression data were analyzed by a 2 × 2 (treatment × group) repeated measures ANOVA.

To test whether sertindole has a differential effect on subjects exhibiting low or high placebo gating measures, subjects were grouped by a median-split procedure into low and high performers. For PPI this split was based on the results of %PPI in the SOA 60 placebo condition ($median_{PPI}$ = 60.92%). Similarly, for the P50 suppression paradigm the median-split was applied using the %P50 suppression scores in the placebo condition ($median_{P50}$ = 43.40%). An alternative grouping by a mean split was considered ($mean_{PPI}$ = 57.50 %; $mean_{P50}$ = 43.31%), but was found to result in almost identical PPI groups, differing only by three subjects, and virtually same P50 groups, differing only by one subject.

CANTAB was recorded successfully in all 30 subjects. Separate two-way ANOVAs with group (separately for P50 and PPI low and high subgroups) and treatment were used to examine the effect of sertindole on the performance of MOT and RVP CANTAB tasks. For the SWM task, the additional factor "difficulty" was introduced.

Similarly, differences in SCL-90 global factor scores between the high and low gating subgroups were assessed by separate repeated measures ANOVA.

For all statistical tests, the significance level was set to $p < 0.05$. Post-hoc pair-wise comparisons were conducted using Fisher's Least Significant Difference (Fisher LSD). In the case of significant effects, the effect size expressed as partial eta-squared (η_p^2) was calculated. For the potential commonalities between PPI and P50 suppression and for the relationships between CANTAB scores and gating measures, Pearson correlations were calculated. Due to the high number of correlations (47) examined, alpha for the Pearson correlations was set to $p < 0.001$.

Results

Subjects Demographics and Psychometric measures

The low and high subgroups, stratified according to either PPI or P50 suppression, did not differ in age, IQ, or alcohol or nicotine consumption. Furthermore, the groups did not differ in the SCL-90 global indices or subscale scores (see Tab. 1 and Tab. 2).

Table 1: Demographic characteristics and SCL-90 scores of the subjects stratified into low and high PPI groups

	Low group (n=11)		High group (n=11)		main effect of group	
Psychometric	Mean	SE	Mean	SE	F	p
Age	20.55	3.24	24.45	1.17	1.29	0.27
IQ*	113.27	2.91	115.27	4.09	0.16	0.7
Nicotin (cigarettes/day)	4.00	1.88	3.64	1.91	0.02	0.89
Alcohol (dl/week)	3.09	1.25	5.57	1.40	1.74	0.2
SCL-90 Global Indices:						
Global Sverity Index (GSI)	0.30	0.10	0.19	0.04	1.20	0.29
Positive Symptom Total (PST)	18.91	5.02	13.64	2.69	0.86	0.37
Positive Symptom Distress Index (PSDI)	1.29	0.10	1.22	0.06	0.31	0.58
SCL-90 Symptom Subscales:						
Somatization	0.20	0.08	0.20	0.04	0.01	0.93
Obsessive-Compulsive	0.46	0.15	0.39	0.10	0.16	0.69
Interpersonal Sensitivity	0.30	0.14	0.11	0.04	1.64	0.22
Depression	0.43	0.12	0.22	0.08	1.97	0.18
Anxiety	0.30	0.09	0.19	0.06	1.02	0.33
Hostility	0.26	0.12	0.15	0.07	0.57	0.46
Phobic Anxiety	0.19	0.09	0.03	0.02	3.48	0.08
Paranoid Ideation	0.32	0.13	0.15	0.05	1.41	0.25
Psychoticism	0.20	0.09	0.08	0.04	1.54	0.23

* measured by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl 1999)

Table 2: Demographic characteristics and SCL-90 scores of the subjects stratified into low and high P50 groups

	Low group (n=13)		High group (n=12)		main effect of group	
Psychometric	Mean	SE	Mean	SE	F	p
Age	22.15	2.17	21.75	2.18	0.02	0.9
IQ*	113.08	2.62	111.17	3.50	0.2	0.66
Nicotin (cigarettes/day)	2.62	1.07	4.50	2.16	0.64	0.43
Alcohol (dl/week)	4.29	1.23	4.92	1.36	0.12	0.73
SCL-90 Global Indices:						
Global Sverity Index (GSI)	0.24	0.09	0.21	0.05	0.05	0.82
Positive Symptom Total (PST)	15.33	4.86	14.67	2.58	0.01	0.9
Positive Symptom Distress Index (PSDI)	1.24	0.07	1.24	0.09	0.01	0.97
SCL-90 Symptom Subscales:						
Somatization	0.19	0.07	0.20	0.05	0.01	0.93
Obsessive-Compulsive	0.38	0.13	0.41	0.12	0.02	0.89
Interpersonal Sensitivity	0.23	0.14	0.16	0.04	0.27	0.61
Depression	0.29	0.11	0.31	0.09	0.02	0.89
Anxiety	0.24	0.09	0.18	0.05	0.31	0.58
Hostility	0.22	0.11	0.19	0.06	0.05	0.83
Phobic Anxiety	0.12	0.08	0.07	0.04	0.28	0.6
Paranoid Ideation	0.26	0.12	0.15	0.06	0.68	0.42
Psychoticism	0.14	0.09	0.09	0.03	0.30	0.59

* measured by the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl 1999)

Prepulse Inhibition Paradigm

Startle reactivity. Startle amplitude between the low and the high subgroup exhibited a statistical trend for higher startle in the low PPI subgroup. As expected, startle amplitude significantly diminished over the three blocks of the test session. Post hoc pair-wise comparisons revealed no differences in startle reactivity in relation to treatment condition and block between the two groups. Moreover, treatment with sertindole exhibited a statistical trend for reduced startle reactivity. To further investigate the influence of sertindole on startle reactivity, additional one-way ANOVA of startle reactivity in the PPI-relevant block 2 with factors group and treatment was performed, revealing a significant main effect of treatment [$F(1,20) = 10.49$, $p < 0.01$, $\eta_p^2 = 0.34$] but no significant interaction (group x treatment). Nevertheless, in accordance with our a priori hypotheses that sertindole may modulate PPI differentially in subjects with high or low baseline PPI, and to control a potential influence of baseline startle, post-hoc pair-wise comparisons revealed a significant startle decrease for the high group in respect to the treatment with sertindole ($p < 0.05$), while just a statistical trend was found for a decrease of startle in the low subgroup ($p = 0.09$) and no group differences were found within the same condition (placebo vs. sertindole). NS trials did not differ between the low and high subgroups and were not affected by sertindole treatment.

Prepulse Inhibition. %PPI was significantly different between the two groups due to the median-splitting of subjects into low and high sensorimotor gaters. As expected, there was a significant main effect of SOA. Moreover, results of the ANOVA revealed a significant treatment × group interaction. Post-hoc pair-wise comparisons revealed that sertindole significantly increased %PPI in the low subgroup ($p < 0.05$) while it decreased it in the high subgroup ($p < 0.05$). There was no significant interaction for treatment × SOA × group. Nevertheless, based on our a priori hypotheses that sertindole would modulate PPI differentially in subjects with high or low baseline %PPI levels and due to the findings of our earlier study, where clozapine influences PPI in low gating subjects at short SOA (Vollenweider et al., 2006), post-hoc pair-wise comparisons were performed, revealing a %PPI increase for the low group in respect to the SOA 60 ($p < 0.05$) and sertindole treatment condition, while not attenuating PPI significantly in the high group respectively in other SOA conditions in the low group (Fig. 1). Additional analysis was done by the use of %P50 suppression group splitting for PPI. Except for SOA [$F(2,36) = 25.25$, $p < 0.001$, $\eta_p^2 = 0.58$], no significant main effects or interactions were found.

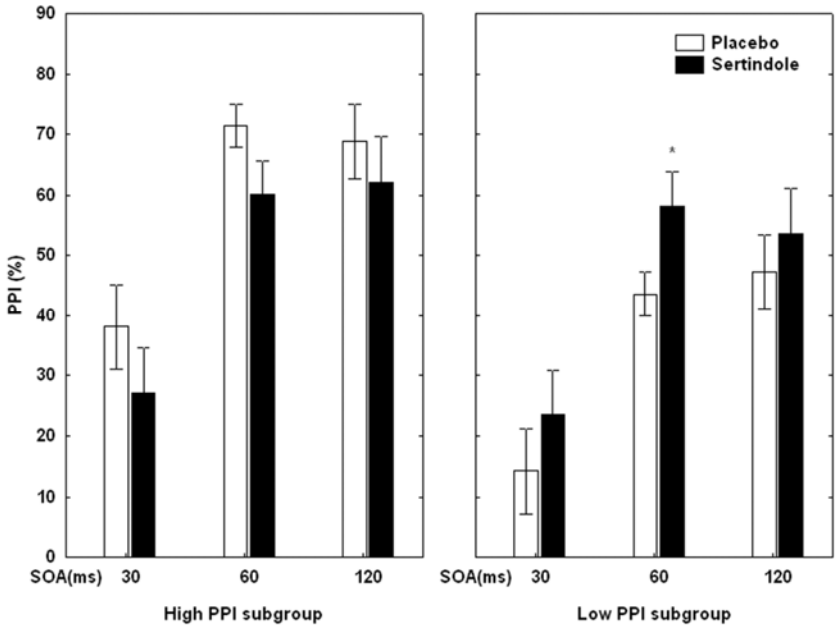

Figure 1. Percentage PPI at the three prepulse-pulse conditions (SOA: 30, 60, and 120 ms) in the low and the high PPI subgroup during placebo (white bars) and sertindole (black bars) treatment. Error bars refer to ±SE.

PPF induced by the SOA condition of 2000 ms did not differ between the low and high subgroups and was not affected by sertindole treatment.

Habituation. There were no significant treatment effects or any significant interactions between the two subgroups on habituation of the startle reflex. Further neurophysiological characteristics of PPI assessment are summarized in Tab. 3.

Table 3: PPI characteristics of low and high gating groups receiving treatment with placebo oder sertindole

	Placebo				Sertindole				main effect of group			main effect of treatment			group x treatment interaction		
	Low group (n=11)		High group (n=11)		Low group (n=11)		High group (n=11)										
Electrophysiology	Mean	SE	Mean	SE	Mean	SE	Mean	SE	F	p	η_p^2	F	p	η_p^2	F	p	η_p^2
PPI paradigm																	
Startle amplitude LN transformed (µV)																	
115 dBA[a]									3.57	0.07	0.15	3.61	0.07	0.15	0.02	0.89	
Block 1	5.24	0.21	4.47	0.20	4.81	0.23	4.34	0.21									
Block 2	4.67	0.19	4.25	0.21	4.47	0.25	3.94	0.23									
Block 3	4.22	0.33	3.69	0.29	4.23	0.38	3.59	0.21									
Non-stimulus	1.12	0.11	0.89	0.09	1.15	0.18	0.86	0.10	3.92	0.06		0.01	1.00		0.10	0.76	
Habituation																	
115 dBA (%)	52.19	10.07	48.40	7.28	5.27	33.33	44.35	8.26	1.04	0.32		1.77	0.20		1.25	0.28	
Inhibition (%)																	
115 dBA[b]									**9.50**	**<0.01**	**0.32**	0.01	0.94		**9.99**	**<0.01**	**0.33**
SOA 30 ms	14.16	8.28	38.10	5.38	23.60	8.35	27.18	6.20									
SOA 60 ms	43.58	4.68	71.41	2.09	58.25	5.61	60.11	5.64									
SOA 120 ms	47.28	6.75	68.82	5.56	53.57	8.41	62.03	6.75									
SOA 2000 ms	-15.01	9.04	6.86	5.45	10.67	7.66	10.45	7.18	2.96	0.10		3.01	0.10		1.71	0.21	

[a] Repeated measures ANOVA including factor "block". Significant main effect of block [F(2,40)=34.36, p<0.001, η_p^2=0.63].

[b] Repeated measures ANOVA including factor "SOA". Significant main effect of SOA [F(2,40)=28.83, p<0.001, η_p^2=0.59].

P50 Suppression Paradigm

P50 amplitude. There was a significant main effect of stimulus number (S_1 vs. S_2), confirming the occurrence of P50 suppression. The interaction of group x treatment reached a statistical

trend level. Moreover, the interactions of stimulus number x group and stimulus number x treatment x group attained statistical significance. Post-hoc testing revealed that sertindole decreased the amplitude elicited by S_2 in low P50 subgroup ($p < 0.001$) while it increased it in the high P50 subgroup ($p < 0.01$). No such effect in regard to treatment was found for the amplitude elicited by S_1. Furthermore, in the high subgroup, S_1 and S_2 amplitudes differed significantly in both the placebo ($p < 0.001$) and sertindole conditions ($p < 0.001$), while in the low subgroup the 2 amplitudes differed only in the sertindole condition ($p < 0.001$). This finding confirms that sertindole increased P50 suppression in the low group due to an increased proportion of the two amplitudes of the 2 stimuli.

P50 suppression. The low and high groups differed in P50 suppression, indexed by percent suppression, as forced by the splitting of the subject group into low and high P50 gaters. No significant main effect of treatment was found. Moreover, the interaction between treatment and group attained significance. Post-hoc testing revealed that sertindole increased P50 suppression significantly in the low group ($p < 0.01$) while reducing the high group's gating performance ($p < 0.05$). Same as for PPI, additional analysis was done using the PPI group splitting for %P50 suppression. No significant main effects or interactions were found, clarifying that a group splitting into high and low subjects did not lead to a regression to the mean.

P50 Latency. No significant main effects or interactions were found for the factor latency. All results are summarized in Tab. 4.

Table 4: P50 supression characteristics low and high gating groups receiving treatment with placebo oder sertindole

	Placebo				Sertindole										
	Low group (n=13)		High group (n=12)		Low group (n=13)		High group (n=12)		main effect of group			main effect of treatment		group x treatment interaction		
Electrophysiology	Mean	SE	Mean	SE	Mean	SE	Mean	SE	F	p	η_p^2	F	p	F	p	η_p^2
P50 suppression paradigm																
Amplitudes (µV) SQR-transformed																
P50[a,b]									0.43	0.52		0.01	0.96	4.08	0.06	0.15
Conditioning stimulus (s1)	1.05	0.09	1.14	0.09	1.09	0.11	1.12	0.07								
Test stimulus (s2)	0.95	0.09	0.52	0.09	0.69	0.10	0.75	0.07								
P50 Suppersion (%)	14.39	8.90	74.65	5.36	49.87	12.13	49.51	8.46	**8.13**	**< 0.01**	**0.26**	0.45	0.51	**15.64**	**< 0.01**	**0.41**
Latency (ms)																
P50									1.240	0.28		0.27	0.61	0.13	0.72	
Conditioning stimulus (s1)	62.95	1.52	62.83	1.54	63.55	2.14	62.50	1.42								
Test stimulus (s2)	59.19	3.06	64.13	2.52	61.30	2.70	64.94	1.95								

[a] Measures ANOVA including factor "stimulus number". Significant main effect of stimulus number [$F(1,23)=80.16$, $p<0.001$, $\eta_p^2=0.78$].

[b] Measures ANOVA including factor "stimulus number". Significant group x stimulus number interaction [$F(1,23)=9.07$, $p<0.01$, $\eta_p^2=0.28$] and group x stimulus number x treatment interaction [$F(1,23)=16.30$, $p<0.001$, $\eta_p^2=0.41$].

Neuropsychological Testing

The high and low PPI subgroups differed in *strategy score* of the SWM task, indicating superior performance by the high PPI subgroup. Moreover, a significant interaction of

treatment x difficulty was found for SWM *between errors* was found. Post hoc comparisons revealed a significant increase of errors in both groups in the most difficult condition under sertindole treatment ($p < 0.01$). There were no further differences in cognitive performance in the other tests between the two PPI subgroups (see Tab. 5).

Table 5: Neuropsychological characteristics of the low and high PPI subgroups receiving treatment with placebo and sertindole

	Placebo				Sertindole										
	low group (n=11)		high group (n=11)		low group (n=11)		high group (n=11)		Main effect of group			Main effect of treatment		Group x treatment interaction	
CANTAB tasks	Mean	SE	Mean	SE	Mean	SE	Mean	SE	F	p	η_p^2	F	p	F	p
MOT[1]															
Latency (ms)	799.22	46.60	720.32	40.38	846.15	50.41	756.55	54.12	2.07	0.17		1.43	0.25	0.02	0.88
RVP[2]															
A'	0.96	0.01	0.97	0.01	0.95	0.01	0.96	0.01	0.28	0.60		0.68	0.42	0.12	0.73
B'	0.96	0.01	0.92	0.03	0.95	0.02	0.74	0.18	1.18	0.29		0.79	0.39	0.53	0.48
Latency (ms)	406.56	22.98	408.40	17.36	422.30	37.52	406.40	19.16	0.05	0.83		0.19	0.67	0.31	0.59
Total hits	22.27	1.27	23.36	0.68	22.00	1.52	22.64	1.16	0.30	0.59		0.67	0.42	0.14	0.71
SWM[3]															
Between errors[a]									1.46	0.24		0.47	0.50	0.01	0.95
Difficulty level 1	0.18	0.12	0.09	0.09	0.27	0.27	0.09	0.09							
Difficulty level 2	3.82	1.63	2.09	1.23	1.73	0.94	0.82	0.38							
Difficulty level 3	6.91	3.19	4.36	1.19	10.45	2.75	6.91	1.58							
Strategy	31.55	1.55	26.18	1.59	29.45	1.71	25.64	1.64	**4.58**	**<0.05**	**0.19**	2.59	0.12	0.89	0.36
Total errors	11.00	4.13	6.82	1.78	14.18	4.06	8.00	1.86	1.76	0.20		0.98	0.33	0.21	0.66

[1]Motor screening , [2]Rapid visual information processing, [3]Spatial working memory

[a]Repeatet measures ANOVA including factor "difficulty". Significant main effect of difficulty [$F(2,40)=19.80$, $p<0.001$, $\eta_p^2=0.50$] and significant treatment x difficulty interaction [$F(2,40)=5.19$, $p<0.01$, $\eta_p^2=0.20$]

Analyzing cognitive performance in CANTAB tasks according to high and low P50 subgroups revealed several treatment effects, dependent on group affiliation (see Tab. 6). Sertindole decreased the high subgroup's performance in the RVP task, as indicated by a significant group x treatment interaction, indexed as well by *A'*, and *Total hits*. Therefore, separate post hoc comparison for both measures showed significant decreases for the high group performance ($p < 0.05$) while no significant effect was found for the low group. Moreover, treatment with sertindole led to a significantly better performance in SWM *strategy score*, indicated by a significant main effect of treatment. Beyond that, a worse performance under sertindole condition in SWM task is denoted by a significant interaction of the factors treatment x difficulty in SWM *between errors*, and a significant post hoc comparison indicating significantly worse performance in the most difficult condition under sertindole treatment ($p < 0.05$).

Table 6: Neuropsychological characteristics of the low and high P50 subgroups receiving treatment with placebo and sertindole

	Placebo				Sertindole				Main effect of group		Main effect of treatment			Group x treatment interaction		
	low group (n=13)		high group (n=12)		low group (n=13)		high group (n=12)									
CANTAB tasks	Mean	SE	Mean	SE	Mean	SE	Mean	SE	F	p	F	p	η_p^2	F	p	η_p^2
MOT[1]																
Latency (ms)	812.30	51.18	704.78	29.06	841.71	39.22	787.32	45.67	2.47	0.13	3.29	0.08		0.74	0.40	
RVP[2]																
A'	0.96	0.01	0.97	0.01	0.96	0.01	0.95	0.01	0.01	0.93	2.47	0.13		**5.34**	**<0.05**	**0.19**
B'	0.94	0.02	0.70	0.22	0.57	0.24	0.91	0.05	0.09	0.77	0.23	0.64		3.33	0.09	
Latency (ms)	392.20	15.41	415.04	23.64	417.78	25.49	406.73	28.58	0.04	0.85	0.42	0.52		1.64	0.21	
Total hits	22.77	0.85	24.00	0.93	23.15	1.13	22.08	1.32	0.00	0.96	2.48	0.13		**5.59**	**<0.05**	**0.20**
SWM[3]																
Between errors[a]									0.25	0.62	0.08	0.79		0.01	0.93	
Difficulty level 1	0.15	0.10	0.08	0.08	0.23	0.23	0.00	0.00								
Difficulty level 2	4.54	1.73	1.42	0.71	1.85	0.80	0.92	0.47								
Difficulty level 3	5.08	2.26	6.25	2.49	8.08	2.66	7.58	1.25								
Strategy	28.46	1.82	29.17	1.37	28.08	1.57	26.58	1.45	0.03	0.85	**4.98**	**0.04**	**0.18**	2.73	0.11	
Total errors	9.85	3.65	7.92	2.74	11.39	3.84	8.92	1.34	0.33	0.57	0.33	0.57		0.01	0.90	

[1]Motor screening , [2]Rapid visual information processing, [3]Spatial working memory

[a]Repeatet measures ANOVA including factor "difficulty". Significant main effect of difficulty [$F(2,46)=20.18$, $p<0.001$, $\eta_p^2=0.47$] and difficulty x treatment interaction [$F(2,46)=3.47$, $p< 0.05$, $\eta_p^2=0.13$].

Discussion

To our knowledge, this is the first study investigating the influence of sertindole on gating measures in humans. The current results revealed that sertindole increases PPI and P50 suppression in healthy subjects exhibiting low baseline PPI low baseline P50 suppression respectively. On the other hand, sertindole attenuated PPI and P50 suppression in subjects exhibiting high levels of baseline gating. Cognitive performance as measured by a subset of test from the CANTAB battery was not impaired by sertindole, which is in contrast to previous studies with other antipsychotics (Csomor et al., 2008a; McCartan et al., 2001; Vollenweider et al., 2006). Furthermore, subjects exhibiting low PPI performed significantly worse in SWM strategy score compared to subjects with high PPI, which is a replication of previous findings (Bitsios et al., 2006; Csomor et al., 2008a; Giakoumaki et al., 2006).

Prepulse Inhibition

In accordance with previous studies investigating the effect of atypical antipsychotic medications on sensorimotor gating (Swerdlow et al., 2006b; Vollenweider et al., 2006), treatment with sertindole increased PPI in subjects exhibiting low baseline gating.

Even though the present results of a PPI-increasing effect induced by atypical antipsychotics in healthy volunteers with low baseline gating are in line with previous studies, this effect seems not as pronounced as seen with clozapine (Vollenweider et al., 2006) or quetiapine (Swerdlow et al., 2006b). Sertindole significantly increased low levels of PPI primary at the SOA 60 ms condition, comparable with clozapine increasing low PPI level at SOA 60 and 120 ms

(Vollenweider et al., 2006), while quetiapine exerted its elevating properties at short SOA conditions of 20 and 30 ms (Swerdlow et al., 2006b). PPI of the present low subgroup under placebo condition (43.58 ±4.68) is comparable to that of our previous study with haloperidol ($mean_{SOA60}$ = 43.8 ±13.8%) (Csomor et al., 2008a) but much higher compared to the studies with clozapine ($mean_{SOA60}$ = 8.8 ±3.3%) (Vollenweider et al., 2006) and quetiapine (%PPI cutoff for low gaters < 16%) (Swerdlow et al., 2006b), adding to the conclusion that the enhancing effect of sertindole was less pronounced compared to the effects of clozapine and quetiapine in previous investigations. Moreover, clozapine lead to a significant reduction of startle reactivity (Vollenweider et al., 2006), which might influenced the measure of sensorimotor gating as indexed by %PPI (Csomor et al., 2008b). Also in the present study there was a trend that sertindole attenuated startle reactivity. A systematic investigation of a potential influence of the magnitude of startle reactivity on PPI has shown that low startle is associated with high PPI and vice versa (Csomor et al., 2008b). However, the influence of the sertindole-induced change in startle reactivity might not solely account for concomitant changes in %PPI. The high group, while being treated with sertindole, showed a significant decrease of startle in the PPI-relevant block 2. Furthermore, no significant decrease of startle was found for the low group. Although startle reactivity was reduced in the low (block 2: from 129.68 to 115.85 μV, non-transformed) and the high (block 2: from 85.43 to 66.16 μV, non-transformed) subgroup to a similar extent, the PPI enhancement was restricted to the low subgroup. Thus it can be concluded that changes in startle did not account for the observed changes in PPI in the current study.

The finding of an enhancing effect of atypical antipsychotics on low PPI gating is in line with the majority of studies showing that patients suffering from schizophrenia treated with atypical antipsychotic medication exhibit PPI values comparable to those of healthy controls (Kumari, Soni, & Sharma, 1999; Kumari, Soni, Mathew, & Sharma, 2000; Kumari, Soni, & Sharma, 2002; Kumari & Sharma, 2002; Kumari et al., 2007; Leumann, Feldon, Vollenweider, & Ludewig, 2002; Oranje, Van Oel, Gispen-De Wied, Verbaten, & Kahn, 2002; Swerdlow et al., 2006a). Nevertheless, other investigations have observed no beneficial effects of either typical or atypical medication on PPI in schizophrenia patients (Duncan et al., 2003a; Duncan et al., 2003b; Mackeprang, Kristiansen, & Glenthoj, 2002; Perry, Feifel, Minassian, Bhattacharjie, & Braff, 2002). Furthermore, the present results are in line with investigations in Wistar rats with low level of PPI (Depoortere et al., 1997) and rats with amphetamine-disrupted PPI (Paabol Andersen & Pouzet, 2001) showing an increasing effect of sertindole on PPI.

Relating to the discussed neurotransmitter systems relevant for schizophrenia spectrum disorders, animal and human studies have shown that PPI can be modulated by dopaminergic, serotonergic, and glutamatergic interventions (Braff, Geyer, & Swerdlow, 2001; Geyer, Krebs-Thomson, Braff, & Swerdlow, 2001; Swerdlow, Braff, & Geyer, 2000). As sertindole has a mixed receptor profile not only acting as a selective D_2-/$5HT_2$-antagonist (Arnt & Skarsfeldt, 1998; Dunn & Fitton, 1996), but also on α1-adrenergic and dopamine D_3 receptors, direct conclusions about the impact of the involved neurotransmitters in the modulation of PPI based on the present study are limited. However, previous findings have shown that presumably the dopamine D_2 antagonistic effect of antipsychotic medication might not account for the increasing effect in low baseline PPI subjects. For instance, chlorpromazine, a potent dopamine D_2 receptor antagonist has no effect on PPI in healthy volunteers (Barrett, Bell, Watson, & King, 2004). In addition, haloperidol (also a selective dopamine D_2 receptor antagonist) does not seem to exert PPI-enhancing properties; while the majority of studies reported no effect on PPI (Abduljawad, Langley, Bradshaw, & Szabadi, 1999; Graham, Langley, Bradshaw, & Szabadi, 2001; Graham, Langley, Balboa Verduzco, Bradshaw, & Szabadi, 2002; Graham et al., 2004; Kumari et al., 1998; Liechti, Geyer, Hell, & Vollenweider, 2001), some studies even found an attenuation (Abduljawad, Langley, Bradshaw, & Szabadi, 1998; Csomor et al., 2008a; Oranje, Kahn, Kemner, & Verbaten, 2004). Moreover, the role an antagonistic action on serotonin receptors in the modulation of PPI seems to be diverse. In contrast to the findings of mainly dopamine D_2 antagonistic acting antipsychotics, clozapine and quetiapine, both having a mixed antagonistic activity at D_2- and $5HT_{2A}$-receptors, do enhance PPI in healthy subjects with low baseline gating capacity (Swerdlow et al., 2006b; Vollenweider et al., 2006). Consequently, we assume that the observed enhancing effect of sertindole on %PPI in healthy subjects exhibiting low baseline sensorimotor gating appears due to the combined impact on serotonergic and dopaminergic neurotransmission. This hypothesis supports descriptive assumptions associating normal gating functions with optimal levels of monoaminergic neurotransmission and synergistic interactions between serotonergic and dopaminergic systems (Mann et al., 2008).

P50 suppression

The present study investigated the effect of an atypical antipsychotic on P50 suppression in healthy volunteers. Comparable to the results of our previous investigation with the typical antipsychotic haloperidol (Csomor et al., 2008a), sertindole increased P50 suppression in subjects exhibiting low P50 gating while attenuating sensory gating in subjects with high P50

suppression. Another study conducted in healthy volunteers revealed that a combination of haloperidol and ketamine lead to a decrement of P50 suppression whereas the application of ketamine alone did not affect P50 suppression (Oranje, Gispen-De Wied, Verbaten, & Kahn, 2002). Until now, studies investigating the effect of antipsychotic medication on P50 suppression in healthy volunteers are scant. The majority of studies investigating schizophrenia patients treated with atypical compared to typical antipsychotics showed improved P50 suppression (Adler et al., 2004; Becker et al., 2004; Light, Geyer, Clementz, Cadenhead, & Braff, 2000) compared to non improvement (Hong et al., 2009). These findings in patients suffering from schizophrenia and the results from studies investigating the influence of various pharmacological manipulations such as dopaminergics (L-dopa, bromocriptine, amphetamine, or tyrosine/phenylalanine depletion), serotonergics (SSRIs such as escitalopram, tricyclic antidepressants such as imipramine, tryptophan depletion, or N,N-dimethyltryptamine), and alkaloidergics (yohimbine) on P50 suppression in healthy volunteers (Adler et al., 1994; Hammer, Oranje, & Glenthoj, 2007; Jensen, Oranje, Wienberg, & Glenthoj, 2008; Light et al., 1999; Mann et al., 2008; Oranje et al., 2004; Riba, Rodriguez-Fornells, & Barbanoj, 2002), suggest that a dysfunction in several neurotransmitter systems might contribute to the observed P50 suppression deficits in schizophrenia. The somewhat inconsistent findings of the involvement of different neurotransmitter in the regulation of P50 suppression in healthy volunteers might be due in part to different reactions to pharmacological interventions according to subjects' baseline levels. Therefore, all of the above cited studies except the one from (Csomor et al., 2008a) did not build groups of high and low baseline P50 suppression subjects. Potential pharmacological effects on P50 suppression might be hidden by the mean of all subjects and one might expect to obtain different results by stratifying subjects according to their baseline gating levels.

There is some indication that atypical antipsychotics may ameliorate sensory gating deficits in schizophrenic patients, as shown for clozapine (Becker et al., 2004; Light et al., 2000; Nagamoto et al., 1996), olanzapine (Light et al., 2000) and risperidone (Light et al., 2000; Yee, Nuechterlein, Morris, & White, 1998). The present results with healthy volunteers lead to the conclusion that sertindole might also lead to a higher P50 suppression in patients suffering from schizophrenia, but this speculation has to be supported by a study investigating the effect of sertindole in schizophrenic patients.

Furthermore, groups of patients with schizophrenia exhibit deficits in both PPI (Braff et al., 1978; Braff et al., 2001) and P50 suppression (Adler et al., 1982; Baker et al., 1987; Cadenhead, 2002; Light & Braff, 1999; Takahashi et al., 2008). Nevertheless, it cannot be

concluded that individual patients with schizophrenia exhibit deficits in both forms of gating, since both the present results and many other observations demonstrate that themeasures are not correlated in either patients or healthy volunteers (Braff, Light, & Swerdlow, 2007; Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004; Light & Braff, 2001; Oranje, Geyer, Bocker, Leon, & Verbaten, 2006; Schwarzkopf, Lamberti, & Smith, 1993). For a detailed review of the literature see (Braff & Light, 2005; Light & Braff, 1999; Oranje et al., 2006; Patterson et al., 2008; Swerdlow, Weber, Qu, Light, & Braff, 2008).

Cognitive Performance

It is noteworthy that high and low PPI subjects performed differentially in a test of spatial working memory as indexed by the SWM strategy score. Subjects exhibiting high PPI chose a better strategy in solving the problem while performances in total and between errors did not differ significantly. We recently reported that subjects with low and high PPI significantly differ in their performance in the SWM task of CANTAB (Csomor et al., 2008a). High PPI levels predicted not only superior strategy formation, furthermore, a significant negative correlation between strategy score and PPI at SOA 60 level was found (Csomor et al., 2008a). Moreover, a significant negative correlation between strategy score and PPI was found by others (Giakoumaki et al., 2006). Contrary to our previous findings (Csomor et al., 2008a), there were no group differences in SWM error scores, leading to the conclusion, that even though the high PPI group chose a superior strategy, there were no performances differences between the two groups. The absence of performance differences might be an explanation for why no correlation between strategy score and PPI was observed in the present study. Furthermore, performance in SWM relies on integrity and efficiency of specific cognitive domains, e.g. relying on prefrontal cortical functioning, and therefore supports the assumption of an involvement of this area in the modulation of PPI which is supported from animal studies (Bitsios et al., 2006; Csomor et al., 2008a; Giakoumaki et al., 2006; Swerdlow et al., 2000; Swerdlow, Geyer, & Braff, 2001; Swerdlow et al., 2008). Therefore, the present result is a notable replication of the findings of our earlier study, and the assumption of a presumable role of the prefrontal cortex in the modulation of PPI, is supported by the different performance of high and low baseline PPI subjects in these cognitive domains. Both human and animal investigations have considered the degree to which PPI and cognition are directly associated as reduced/impaired PPI is associated with decreased cortical task-related activation in schizophrenia (Geyer, 2006; Molina et al., 2010) and perfusion measured with single photon-emission tomography (SPECT) was significantly lower in the prefrontal and premotor regions

of the schizophrenic patients (Scholes & Martin-Iverson, 2009). Moreover, Kedzior, Koch, and Basar-Eroglu (2007) concluded that the relationship between PPI and cognitive performance appears to be mediated by common attentional processes active in both tasks, rather than by common underlying neurophysiological inhibitory processes. Contrary results of no statistically significant correlations between PPI and neuropsychological performance have also reported (Molina et al., 2009).

Furthermore, it can be assumed that superior ability in cognitive performance in this domain is related to more efficient early information processing. Moreover, cognitive deficits in schizophrenia spectrum disorders, especially measured by (pre)frontal tasks and confirmed by an altered neuronal activity, is a undisputable finding (Badcock et al., 2005; Hutton et al., 1998; Manoach, 2003; Minzenberg et al., 2009; Weickert et al., 2000) with great impact on quality of life and functional outcome (Brekke, Kay, Lee, & Green, 2005; Green, 2006).

Compared to the findings with high and low sensorimotor gaters, P50 subgroups did not differ in their cognitive performances which was also the case in our earlier study (Csomor et al., 2008a). Under treatment with sertindole, both groups chose a better strategy in SWM task while performances, as indexed by the amount of errors, was worse at the most difficult condition. Moreover, under sertindole treatment, the high group's performance was decreased in attention and working memory (indicated by A' and total hits in RVP task) while the low group's performance was not affected. Therefore, treatment with sertindole did not lead per se to a general reduction of cognitive performances. Contrary to the present findings, it is more common, that cognitive performance in healthy volunteers is generally diminished by typical or atypical antipsychotic medication, possibly caused by sedative side effects (Csomor et al., 2008a; McCartan et al., 2001; Vollenweider et al., 2006). Sertindole seems to have no effect on muscarinic and histaminic H_1 receptors, and compared to other atypical antipsychotics exerting relatively high occupancy at these receptor sites, sertindole is not linked with anticholinergic side effects (Didriksen, 1995; Didriksen, Kreilgaard, & Arnt, 2006; Didriksen, Skarsfeldt, & Arnt, 2007; Rodefer, Nguyen, Karlsson, & Arnt, 2008; Skarsfeldt, 1996). Therefore, it is less associated with sedation while still having a satisfactory effect on both positive and negative symptoms (Arnt & Skarsfeldt, 1998; Kasper, Hale, Azorin, & Möller, 1999; Kasper, 2008; Perquin & Steinert, 2004; Zimbroff et al., 1997). More evidence for its favorable cognitive profile is coming from studies with rodents (Didriksen, 1995; Didriksen et al., 2006; Didriksen et al., 2007; Rodefer et al., 2008; Skarsfeldt, 1996). While the superior effect of potent $5HT_2$ (and relatively weaker D_2) antagonists on cognitive function has been discussed (Meltzer & McGurk, 1999), further evidence of a better impact on cognitive functions of sertindole is

coming from a study with schizophrenic patients where treatment with sertindole was compared to haloperidol (Gallhofer et al., 2007). Moreover, due to the results of studies with rodents one might speculate that a combination of an absence of antimuscarinic activity and coexistent 5-HT_6 antagonistic activity might represent a key feature of sertindole leading to a positive cognitive profile (Rodefer et al., 2008). In addition, more evidence for the favorable role of 5-HT_6 antagonistic action on cognitive performance has been discussed recently (Dawson, Nguyen, & Li, 2001; Hirst et al., 2006; King, Marsden, & Fone, 2008; Lacroix, Dawson, Hagan, & Heidbreder, 2004; Marcos, Chuang, Gil-Bea, & Ramirez, 2008; Meltzer, 1994; Miguel-Hidalgo, 2001; Schaffhauser et al., 2009; Singer et al., 2009; Upton, Chuang, Hunter, & Virley, 2008; Woolley, Marsden, & Fone, 2004).

Conclusions

The influence of antipsychotics on sensory and sensorimotor gating in healthy volunteers seems to be dependent on baseline gating levels. In summary, there is increasing evidence that mixed D_2 / 5-HT_2 receptor antagonists modulate PPI as well as P50 suppression in a way to enhance it in healthy subjects with low baseline gating in a way comparable as seen in studies with schizophrenia patients. Moreover, both cognitive performance and PPI seems to be dependent on proper prefrontal cortical functioning being supported by the replication of the finding that high PPI gating subjects perform significantly better in SWM strategy score. Furthermore, the results of the present study militates in favor of the concomitant assessment of PPI and P50 suppression as well as cognitive measures while investigating the effect of antipsychotic medication in healthy volunteers stratified into low and high baseline gating subgroups. The combined use of PPI and P50 suppression in a single study might represent excellent tools for translational research. Nevertheless, to gain further evidence of the influence of sertindole on gating functions as well as their relation to psychopathology and cognition, a clinical study in patients suffering from schizophrenia should be undertaken, where the effect of sertindole on the above-mentioned parameters, as well as on psychopathologic symptomatology, should be investigated and compared to other atypical antipsychotic medication in a longitudinal study design.

Conflict of Interest Statement

None of the authors has any conflicts of Interest to declare.

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5. DISCUSSION

5.1. Impaired gating functions in PTSD and ADHD

Functional gating is an important function of the brain, preventing the brain from sensory overload by filtering out irrelevant stimuli. Moreover, a deficit in gating is characterized by a general reduction of the ability to gate intrusive sensory, motor and/or cognitive information (Braff & Geyer, 1990; Geyer et al., 1987). While, sensory gating and sensorimotor gating have been proposed to be endophenotypic biomarkers for schizophrenia spectrum disorders (Adler et al., 1982; Adler et al., 2004; Baker et al., 1987; Braff & Light, 2005; Cadenhead, 2002; Cadenhead, Light, Geyer, McDowell, & Braff, 2002; Geyer, 2006; Gottesman & Gould, 2003; Light & Braff, 1999), deficient gating is not exclusively attributable to schizophrenia spectrum disorders. We showed that PTSD patients as well as ADHD patients showed impaired sensory gating but not sensorimotor gating.

5.1.1. Patients with PTSD as well as patients with ADHD showed no impairment of sensorimotor gating

The results of the study reported in chapter 2 showed that PTSD patients exhibited intact sensorimotor gating which is in line with other studies (Butler et al., 1990; Grillon, Morgan, Davis, & Southwick, 1998b; Lipschitz et al., 2005), while some studies reported impaired sensorimotor gating (Grillon, Morgan, Southwick, Davis, & Charney, 1996; Grillon, Morgan Ill, Davis, & Southwick, 1998a; Ornitz & Pynoos, 1989). A source potentially complicating the comparability and interpretation of PPI between studies might be differences in startle reactivity between groups under comparison. Changes in PPI with concomitant changes in startle amplitude cannot be directly interpreted as a change in sensorimotor gating per se (Braff, Geyer, & Swerdlow, 2001; Csomor et al., 2008c; Swerdlow, Braff, & Geyer, 2000). Even though startle reactivity was elevated in the startle testing session consisting of pulse stimuli only, no between-group difference in regard to startle reactivity was detected in the PPI testing session. Therefore, the absence of a PPI difference between PTSD patients and healthy controls cannot be attributed to divergent startle reactivity between the two groups. Consequently, PPI seems not to be a recommendable psychophysiological measure to support the diagnosis of PTSD.

Furthermore, reported by the study in chapter 3 ADHD patients showed similar sensorimotor gating as do healthy controls. Moreover, the parameter settings used to elicit PPI are comparable to those used in other studies investigating PPI in adult ADHD (115 dB pulse stimulation, at least SOA 30, 60, 120 ms background white noise) (Feifel, Minassian, & Perry, 2009; Hanlon, Karayanidis, & Schall, 2008) supporting the conclusion that ADHD patients have no impairment in sensorimotor gating. However, comorbidity of tic disorder or primary nocturnal enuresis seems to be an important contributor to the diminished PPI observed in these ADHD patients (Castellanos et al., 1996; Ornitz, Hanna, & de Traversay, 1992; Ornitz et al., 1999). Furthermore, PPI deficits were found in patients with Tourette's syndrome, which has a high comorbidity with ADHD disorder (Chase, Geoffrey, Gillespie, & Burrows, 1986; Singer et al., 1993; Peterson et al., 1993). However, the absence of a PPI deficit in ADHD in the reported studies could be due to the use of a passive PPI paradigm since other findings have been reported for active listening paradigms. Moreover, dopamine is believed to play an important role in the pathophysiology underlying ADHD symptomatology (Biederman & Faraone, 2005; Staller & Faraone, 2007) and dopaminergic interventions influence PPI (Braff et al., 2001). Contrary, treatment with methylphenidate (MPH), a stimulant drug acting as a dopamine agonist often used to treat ADHD, enhanced PPI only during attended, but not during ignored stimuli in children suffering from ADHD (Ashare et al., 2010). Adult ADHD patients did not differ from healthy controls in either attended or ignored conditions, nor did stimulant treatment affect their PPI (Hanlon et al., 2008). To this end, the factor attended vs. ignored stimuli has not been tested in the present study. Furthermore, our study showed that adult ADHD patients taking regularly stimulant medication showed rather a decreased than an increased PPI. Consequently, the absence of PPI differences between ADHD patients and controls underlines the absence of a diminished PPI in ADHD. Therefore, attention deficits in adult ADHD cannot be directly associated or related to an impaired sensorimotor gating.

As discussed before, a different parameter setting might be responsible for the divergent findings of sensorimotor gating in PTSD and ADHD. Therefore, the testing session applied in both of the present studies consisted of the recommendation of highly standardized parameter setting coming from schizophrenia research (Braff et al., 2001). Thus, it can be concluded that reduced sensorimotor gating is neither a trait marker of PTSD nor of ADHD. In regard to PPI, it still remains imperative to establish firm experimental parameters for patients' studies enabling effective comparisons of results between different laboratories. While there might be a potential influence of long-time stimulant treatment in ADHD, larger sample size studies with a longitudinal design investigating systematically the influence of medication on PPI in

ADHD while simultaneously reporting psychopathological symptoms and cognitive functions are necessary to investigate potential PPI differences in ADHD patients treated with stimulants compared to those who were not and/or never treated.

5.1.2. PTSD patients but not ADHD patients exhibited increased startle reactivity

While ADHD patients compared to healthy controls showed no differences in startle reaction, patients with PTSD exhibited increased startle reactivity, which is in agreement with previous reports (Butler et al., 1990; Grillon et al., 1998b; Morgan Ill, Grillon, Southwick, Davis, & Charney, 1995; Morgan, Grillon, Southwick, Davis, & Charney, 1996; Orr, Lasko, Shalev, & Pitman, 1995; Pole, 2007; Shalev, Peri, Orr, Bonne, & Pitman, 1997). The absence of an increased startle in PTSD (Carson et al., 2007; Grillon et al., 1996; Jovanovic, Norrholm, Sakoman, Esterajher, & Kozaric-Kovacic, 2008; Metzger et al., 1999; Orr, Solomon, Peri, Pitman, & Shalev, 1997; Orr et al., 2003; Siegelaar et al., 2006), might be attributed to differences in the experimental parameter setting. Therefore, a statistical artifact might account for the reported none differences in startle reaction in some studies using only one intensity to elicit startle reaction, as with a greater number of intensities statistical power increases. While we used four intensities in our PTSD study, almost all of the studies revealing negative results made use of a single (Carson et al., 2007; Griffin, 2008; Jovanovic et al., 2008; Lipschitz et al., 2005; Medina, Mejia, Schell, Dawson, & Margolin, 2001; Metzger et al., 1999; Orr et al., 1997; Orr et al., 2003; Siegelaar et al., 2006) or two (Grillon et al., 1996) stimulus intensities. To this end, the current findings underline the importance of including startle evoking stimuli of multiple intensities to enhance the likelihood for the detection of exaggerated startle in patients suffering from PTSD. Furthermore, the finding of increased startle cannot be attributed to low habituation in the patients, as habituation of the present subjects did not differ between patients and control subjects, as reproduced by others (Carson et al., 2007; Grillon et al., 1996; Lipschitz et al., 2005; Metzger et al., 1999; Morgan III et al. 1995; Orr et al., 1995; Orr et al., 1997; Orr et al., 2003; Shalev et al., 1997; Siegelaar et al., 2006). Thus, it can be concluded that exaggerated startle and diminished habituation, if any, reflect mostly independent neurophysiological alterations. Even though we used only two intensities to evoke startle in the ADHD study, based on our findings and of others (Feifel et al., 2009; Hanlon et al., 2008), we conclude that increased startle as well as altered habituation seem not to be a physiological marker of ADHD. Furthermore, we discussed that state anxiety and a general higher arousal

level of the PTSD patients at the beginning of the test session might have conducted to the differences in startle reaction in the startle paradigm and the absence of such a difference in the PPI session. PTSD Patients might have become accustomed to the laboratory environment during the series of experiments, and consequently, elevated startle in the present PTSD sample would be state anxiety dependent. In this connection, it has been shown that increased startle in PTSD patients has been consistently reported when elicited in settings in which the subject anticipate an aversive event (i.e., fear potentiated startle) (Grillon et al., 1998a; Grillon et al., 1998b; Grillon & Morgan, III, 1999; Medina et al., 2001; Morgan Ill et al., 1995). Furthermore, state anxiety during the testing session was higher in PTSD patients' group compared to the ADHD patients' group (54.54 vs. 49.60), which might explain partly the differences in startle reactivity (e.g. relation between higher state anxiety and increased startle reactivity). Nevertheless, as startle is reflecting a DSM-VI diagnostic criteria for the assessment of PTSD (Sass, Wittchen, & Zaudig, 1998) and not of ADHD, we conclude that increased startle represents an altered neurophysiological response in patients suffering from PTSD and might represent a valuable parameter to support PTSD diagnosis. However, studies with greater sample sizes are needed to investigate whether there is a relation between the severity of PTSD psychopathology and the dimension of startle reactivity.

5.1.3. Patients with PTSD as well as patients with ADHD exhibit impaired sensory gating

The finding of impaired sensory gating in patients suffering from PTSD reported in chapter 2 is in line with the majority of findings previously reported (Ghisolfi et al., 2004; Gillette et al., 1997; Karl, Malta, & Maercker, 2006; Neylan et al., 1999; Skinner et al., 1999). Many studies investigating psychophysiological alterations in PTSD rely on relatively homogenous patient samples like male combat veterans (Butler et al., 1990; Gillette et al., 1997; Grillon et al., 1996; Grillon et al., 1998a; Grillon et al., 1998b; Grillon & Morgan, III, 1999; Jovanovic et al., 2008; Morgan Ill et al., 1995; Neylan et al., 1999; Orr et al., 1995; Orr et al., 1997; Orr et al., 2003; Skinner et al., 1999) or Vietnam nurses (Carson et al., 2007; Metzger et al., 2002). Contrary, the PTSD psychopathology of the cohort studied in the present investigation is based on various traumatic experiences. Therefore, the present findings of impaired P50 gating in PTSD patients seem not to be trauma specific. We conclude that deficient P50 gating, not related to specific trauma or distinct symptom clusters, reflects a robust finding in PTSD patients. Moreover, sensory gating was reduced in ADHD patients reported in chapter 3. Our

finding of reduced sensory gating in ADHD is in contrast to the only previous study investigating P50 suppression in ADHD (Olincy et al., 2000). As discussed in chapter 3 a confounding factor might be a different parameter setting compared to the Olincy et al. (2000) study (e.g. smaller number of stimuli, less intensity), which might be not large enough to generate robust results. Moreover, de Wilde, Bour, Dingemans, Koelman, and Linszen (2007) reported differences in P50 suppression according to the subject's position during electrophysiological recording. While in the present study subjects were sitting in an upright position, in the Olincy et al. (2000) study subjects were in a supine position. Thus, one or more of these differences in the testing conditions may partly account for the diverse finding leading to the conclusion, that, as discussed for PPI, it is imperative to establish firm experimental parameters for P50 suppression enabling effective comparisons of results between laboratories.

Reduced P50 gating in both of our patient groups was due to differences in the amplitudes elicited by S_2, rather than S_1 and therefore can be interpreted as an impairment in central inhibitory activity (Ghisolfi et al., 2004; White & Yee, 1997). In schizophrenia research it has been discussed that high S_2/S_1 ratios (indicating low sensory gating) can result from a deficient response evoked by the S_1 stimulus (e.g. small S_1 amplitude), which is activating both, excitatory and inhibitory mechanisms, or by the S_2 stimulus (e.g. large S_2 amplitude), representing an interference between the inhibitory mechanisms activated by S_1 and the excitatory mechanisms by S_2. The excitatory response reflects the capacity of the neuronal system under study to respond in the absence of any inhibition (Adler et al., 2004). Therefore, the decrement of S_2 reflects the strength of the inhibitory mechanisms, activated by S_1. The interpretation whether both, S_1 and S_2 deficits reflect a form impaired gating is not definitively resolved and needs to be further discussed. Moreover, the overlapping ratios of P50 suppression between different psychiatric patients groups and between healthy controls raise some questions concerning the specificity and stability of sensory gating measured by P50 suppression. It is imperative to answer these questions by the use of a uniformed and established use of parameter setting investigating P50 suppression and its stability over time within the same subjects by the use of a longitudinal study design. Moreover, the inhibition of other components of AEPs (e.g. P30, N100 and P200) has not been studied so extensively within the domain of neurophysiological research in psychiatric patients.

Stewart and coworkers (Stewart & White, 2008) showed that patients suffering from PTSD reported in a self-reported assessment disruption of sensory filtering. Although speculative, this might be reflected on a neurophysiological level by diminished P50 suppression in spite of the absence of deficient PPI as reported above. Moreover, consistent with a previous report

(Metzger et al., 2002), higher SCL-90-R global scores were associated with lower P50 gating. However, the present results and the findings of Metzger et al. (2002) have to be interpreted with caution, since the correlations account only for a limited proportion of the variance. It remains essential to further validate potential relationships between general psychopathology and the magnitude of P50 gating in various patient cohorts. Moreover, the absence of correlations between P50 ratio and PTSD related psychopathology (IES-R and CAPS scores) were also reported by Neylan et al. (1999). Contrary to our findings in PTSD patients, no significant correlations between gating measures and psychological and psychopathological self ratings were found in ADHD patients. Nevertheless, ADHD patients reported significantly more anxiety, depression, and general psychopathological symptoms and described themselves differently in personality factors (neuroticism, agreeableness, and conscientiousness) than the healthy control group.

Concerning structural und functional correlates in ADHD, neuroimagine studies of ADHD suggest that deficits in frontal lobe function and connections between this region and subcortical regions are a key feature of ADHD (Biederman, 2005). Furthermore, regulatory circuits including prefrontal cortex and the basal ganglia are altered in ADHD (Castellanos, 1997; Faraone et al., 2000). These circuits are modulated by dopaminergic innervations, and because of a frontal dopaminergic hypoactivity in ADHD, modulated by stimulant medication (Faraone et al., 2000; Sagvolden, Johansen, Aase, & Russell, 2005). Some authors assume that ADHD can be conceived primarily as a noradrenergic deficiency syndrome with a general underarousal (Abikoff, Courtney, Szeibel, & Koplewicz, 1996) or a deficient maintenance of arousal as the core deficit (Biederman & Spencer, 1999; Brown & McMullen, Jr., 2001). Moreover, involvement of frontal lobe in the generation of P50 suppression has been reported by Weisser et al. (2001) and sensory gating has been associated with prefrontal cortex, the hippocampus, and temporo-parietal regions (Grunwald et al., 2003). In addition, an activation pattern of multiple regions including frontal, temporal, limbic, and parietal regions seems to be involved in high P50 suppression (Knott, Millar, & Fisher, 2009). Therefore, Kurthen et al. (2007) suggest that the early stage of sensory gating already involves a top-down modulation of sensory input by frontal areas, which in turn could be a candidate region for an early cross- or supra-modal aspect of gating. Consequently, an altered frontal functioning, as reported in ADHD, and as a consequence an impaired top-down modulation, may conduct to a diminished sensory gating found in ADHD patients.

Thus, deficient P50 suppression might be a potential promising candidate for an endophenotype marker in PTSD and in ADHD or the vulnerability to their development. Some

of the criterions stated by (Gottesman & Gould, 2003), such as heritability and state-independency, qualifying P50 gating as an endophenotype candidate are fulfilled (Anokhin, Vedeniapin, Heath, Korzyukov, & Boutros, 2007; Hall et al., 2006; Kisley, Olincy, & Freedman, 2001; Kisley et al., 2003). On the other hand, it must be investigated whether non-affected family members of PTSD patients and ADHD patients show reduced P50 suppression at a higher rate than in the general population, and whether it is co-segregating within such families. Furthermore, P50 gating deficits are found in several other psychiatric disorders such as schizophrenia (Adler et al., 1982; Braff, Light, & Swerdlow, 2007; Cadenhead, 2002; De Wilde et al., 2007; Light & Braff, 1999), schizotypal personality disorder (Cadenhead et al., 2002), psychotic bipolar disorder (Hall et al., 2008; Schulze et al., 2007), PTSD (Ghisolfi et al., 2004; Gillette et al., 1997; Holstein, Vollenweider, Jäncke, Schopper, & Csomor, 2010; Neylan et al., 1999; Skinner et al., 1999), and Alzheimer dementia (Thomas et al., 2008). Consequently, P50 gating is not exclusively associated with a specific disorder. Moreover, impaired P50 suppression might be a general and common feature of several psychiatric disorders sharing deficits in attention functions. That reduced P50 gating is not exclusively attributable to PTSD is also reflected by the association with general psychopathology as index by SCL-90 global scores, and the absence of such a relationship with PTSD specific symptomatology.

The low correlations between PPI and P50 suppression in both of our studies confirm again that P50 gating and PPI represent distinct forms of gating, as already reported for both humans and animals elsewhere (Braff et al., 2007; Brenner, Edwards, Carroll, Kieffaber, & Hetrick, 2004; Light & Braff, 2001; Oranje, Geyer, Bocker, Leon, & Verbaten, 2006; Schwarzkopf, Lamberti, & Smith, 1993;). Moreover, the present findings supports the suggestion that PPI and P50 suppression represent different aspects of attention and inhibition (Braff et al., 2007).

Further research is needed to clarify whether P50 gating might reflect an endophenotype marker of ADHD and PTSD. Moreover, longitudinal studies are necessary to evaluate whether these neurophysiological measures have the potential to serve as independent efficacy markers for therapeutic outcome or might even be instrumental as vulnerability predictors for the development of PTSD following traumatic experience. It remains fundamental to assess established parameters for patients' studies comparable to those coming from schizophrenia research to achieve constant and comparable and study overlapping data. Thus, sensorimotor and sensory gating measures can be used as informative and independent neurophysiological markers for studies investigating neuropsychiatric disorders and may well constitute separable endophenotypes. Further research is needed, including double-blind randomized longitudinal

studies measuring ADHD patients before and while treated with stimulant medication, to investigate long lasting influences of stimulant medication on PPI in ADHD, and to evaluate whether operational measures of sensory gating have the potential to serve as efficacy markers for therapeutic outcome.

5.1.4. No relation between impaired sensory gating and cognitive performance was found in ADHD patients

As predicted, ADHD patients performed worse compared to healthy controls in cognitive measures of attention, spatial working memory, and executive functions (planning and strategy). These results are in line with previous findings. Impaired sustained attention is a common and robust finding in ADHD (Calis, Grothe, & Elia, 1990; Gallagher & Blader, 2001; Johansen, Aase, Meyer, & Sagvolden, 2002; Rodriguez-Jimenez et al., 2006). Moreover, decreased working memory (e.g. SWM) (Barkley, 1997; Dowson et al., 2004; Gallagher & Blader, 2001; Levy, 2009; McLean et al., 2004; Rodriguez-Jimenez et al., 2006) and difficulties in executive functioning (Greene, Braet, Johnson, & Bellgrove, 2008; McLean et al., 2004; Mercugliano, 1999; Rodriguez-Jimenez et al., 2006; Seidman, Biederman, Weber, Hatch, & Faraone, 1998) are often reported.

Imaging studies indicate that alterations in the constitution and function of prefrontal cortex, cerebellum, and their network connections, including the lateral prefrontal cortex, the dorsal anterior cingulate cortex, the caudate nucleus, and putamen are important findings in ADHD (Mercugliano, 1999; Schneider, Retz, Coogan, Thome, & Rosler, 2006). Rather than a fixed dysfunction, functional disconnections between subcortical, frontal and posterior regions are assumed, while this dysfunction may lead to inactivation, or insufficient engagement, of prefrontal and frontal regions (Wasserstein & Lynn, 2001). In addition, right frontal patients as well as ADHD patients showed a significant association between SWM and response inhibition, making it plausible, that a common pathological process rather than distinct deficits may be responsible for the impairments in ADHD (Clark et al., 2007).

At a neurobiological level, due to the ameliorating effect of stimulant medications (e.g. dopamine agonists as MPH) in ADHD treatment, a dysfunction in the dopamine system may contribute to ADHD symptoms as well as impaired cognitive performance (Johansen et al., 2002). Furthermore, dopamine acts as a key neurotransmitter in the brain and seems to be a modulator of different aspects of cognitive brain functions (Nieoullon, 2002). Numerous

studies have shown its regulatory role for motor and limbic functions, as well as on a behavioral level, giving rise to deficient sustained attention, hyperactivity, motor abnormalities, and impulsiveness (Johansen et al., 2002). These features are comparable to observation of children suffering from ADHD (Kempton et al., 1999).

While there was no better performance within the subgroup of patients, taking stimulant medication prior to the our study, there is evidence, that long-term taking of stimulant medications improves performances in visual-spatial working (it reduces errors but has no effect on strategy score) (Goldberg et al., 2005), recognition memory (Coghill, Rhodes, & Matthews, 2007), SWM (Turner, Blackwell, Dowson, McLean, & Sahakian, 2005), and sustained attention (Turner et al., 2005). Furthermore, it has been reported that a single acute dose of MPH had no improving effect (Rhodes, Coghill, & Matthews, 2006). Moreover, some authors assume that ADHD can be conceived primarily as a noradrenergic deficiency syndrome with a general underarousal (Abikoff et al., 1996) or a deficient maintenance of arousal as the core deficit, resulting in an impairment of information processing and deficit of attention (Biederman & Spencer, 1999; Brown & McMullen, Jr., 2001). For this reason the pharmacologic management of ADHD relies on agents that affect dopaminergic and noradrenergic neurotransmission, namely, the stimulants, antidepressants, and antihypertensives. The most commonly used stimulants for the treatment of ADHD are MPH and amphetamine (Spencer, 2007; Spencer, Biederman, & Mick, 2007; Wolraich et al., 2005). Although treatment of cognitive deficits and psychopathologic symptoms in ADHD with MPH is well established not all of the treated patients show the expected positive response. About 10-30% of the patients do not respond to treatment with MPH (Gonzalez de, Cardo, & Servera, 2006; Kemner, Starr, Ciccone, Hooper-Wood, & Crockett, 2005; Pelham et al., 2001; Stein et al., 2003). Moreover, treatment with classical stimulants (which primarily increase dopaminergic activity) produce a number of physical side effects. Therefore the development and evaluation of alternative treatments is timely and warranted.

No relation was found between gating measures and cognitive performances. Contrary to recent findings with healthy volunteers (Bitsios, Giakoumaki, Theou, & Frangou, 2006; Csomor et al., 2008a; Giakoumaki, Bitsios, & Frangou, 2006), where a relation between sensorimotor gating and cognitive performance was found, our ADHD study revealed no significant and relatively low correlations between these measures.

5.2. Pharmacological influences on sensory and sensorimotor gating in healthy volunteers

5.2.1. Sertindole increases sensorimotor gating in healthy volunteers with low baseline PPI

In accordance with previous studies investigating the effect of atypical antipsychotic medication, more precisely selective D_2-/$5HT_2$-antagonists, on sensorimotor gating (Swerdlow, Talledo, Sutherland, Nagy, & Shoemaker, 2006b; Vollenweider, Barro, Csomor, & Feldon, 2006) sertindole increases PPI in subjects exhibiting low baseline gating. Even though the present results of a PPI-increasing effect induced by atypical antipsychotics in healthy volunteers with low baseline gating are in line with previous studies, this seems not as pronounced as seen with other antipsychotic compounds as clozapine (Vollenweider et al., 2006) or quetiapine (Swerdlow et al., 2006b).

Compared to our finding of an increasing effect of sertindole at SOA 60 ms condition, at which diminishment is commonly reported in schizophrenia (Csomor et al., 2008b; Kumari & Sharma, 2002), quetiapine, elevates PPI significantly at short SOA conditions of 20 and 30 ms but not at 60 and 120 ms (Swerdlow et al., 2006b). No assumption of a potential effect of quetiapine on subjects exhibiting high baseline PPI could be made because Swerdlow et al. (Swerdlow et al., 2006b) examined only subjects with low baseline PPI. Moreover, Clozapine increases low PPI level at SOA 60 and 120 ms and does not seem to affect subjects with high baseline PPI (Vollenweider et al., 2006). Furthermore, clozapine conducted to a significant reduction of startle reactivity (Vollenweider et al., 2006), which might had influenced the measure of sensorimotor gating as indexed by %PPI (Csomor et al., 2008c), while sertindole just attenuated startle reactivity on a statistical trend level. However, we conclude in the study of chapter 4 that the influence of the sertindole-induced change in startle reactivity might not account for concomitant increase of %PPI in the low group.

Further evidence of a beneficial effect of atypical antipsychotics on PPI is coming from studies showing that patients suffering from schizophrenia have equitable PPI values as healthy controls while treated with atypical neuroleptic medication (Kumari, Soni, & Sharma, 1999; Kumari, Soni, Mathew, & Sharma, 2000; Kumari, Soni, & Sharma, 2002; Kumari & Sharma, 2002; Kumari et al., 2007; Leumann, Feldon, Vollenweider, & Ludewig, 2002; Oranje, Van Oel, Gispen-De Wied, Verbaten, & Kahn, 2002; Swerdlow et al., 2006a), whereas controversy effects of no beneficial effect of either, typical or atypical medication is coming from other studies (Duncan et al., 2003a; Duncan et al., 2003b; Mackeprang, Kristiansen, & Glenthoj, 2002; Perry, Feifel, Minassian, Bhattacharjie, & Braff, 2002). Furthermore, the present results are in line with investigations in Wistar rats with low level of PPI (Depoortere et al., 1997) and

rats with amphetamine-disrupted PPI (Paabol Andersen & Pouzet, 2001) showing an increasing effect of sertindole on PPI.

Direct conclusions about the impact of the involved neurotransmitters in the modulation of PPI as gained by the present study are limited, as sertindole has a mixed receptor profile not only acting as a selective D_2-/$5HT_2$-antagonist (Arnt & Skarsfeldt, 1998; Dunn & Fitton, 1996), but also on α1-adrenergic and D_3 receptors. However, previous findings have shown that presumably the D_2 antagonistic effect of antipsychotic medication might not account for the increasing effect in low baseline PPI subjects. For instance, chlorpromazine a potent D_2 receptor antagonist has no effect on PPI in healthy volunteers (Barrett, Bell, Watson, & King, 2004). In addition, haloperidol (also a selective D_2 receptor antagonist) does not seem to exhibit PPI enhancing properties; while the majority of studies reported no effect on PPI (Abduljawad, Langley, Bradshaw, & Szabadi, 1999; Graham, Langley, Bradshaw, & Szabadi, 2001; Graham, Langley, Balboa Verduzco, Bradshaw, & Szabadi, 2002; Graham et al., 2004; Kumari et al., 1998; Liechti, Geyer, Hell, & Vollenweider, 2001), some studies even found an attenuation (Abduljawad, Langley, Bradshaw, & Szabadi, 1998; Csomor et al., 2008a; Oranje, Kahn, Kemner, & Verbaten, 2004). Moreover, selective dopamine depletion had no effect on PPI (Mann et al., 2008). However, the role of an antagonistic action on serotonin receptors in the modulation of PPI seems to be diverse. In contrast to the findings of mainly D_2 antagonistic acting antipsychotics, clozapine and quetiapine, both having a mixed antagonistic activity at D_2- and $5HT_{2A}$-receptors, do enhance PPI in healthy subjects with low baseline gating capacity (Vollenweider et al., 2006; Swerdlow et al., 2006b). Moreover, selective serotonin depletion conducted to a decreased PPI as well as a combined depletion of serotonin and dopamine (Mann et al., 2008). In addition, imipramine, a dual-acting antidepressant blocking central noradrenaline reuptake and central serotonin reuptake, significantly decreased PPI (Hammer, Oranje, & Glenthoj, 2007). As a result of comparing the effects of a variety of antidepressant drugs (e.g. tricyclics, serotonin-selective reuptake inhibitors (SSRI), and norepinephrine-selective uptake inhibitors), Braff et al. (2001) concluded that antidepressants have no clear effects on PPI neither in humans nor in animals. Moreover, the role of serotonin in the modulation of PPI seems to be diverse. Therefore, the application of psilocybin, a mixed $5HT_1$ and $5HT_2$ agonist, increases PPI (Gouzoulis-Mayfrank et al., 1998) or seems to have opposites effects at shorter (decrease) vs longer (increase) ISIs (Vollenweider, Csomor, Knappe, Geyer, & Quednow, 2007). In addition, the serotonin 5-HT_2 agonist N,N-dimethyltryptamine had no significant effect on PPI (Heekeren et al., 2007; Riba, Rodriguez-Fornells, & Barbanoj, 2002), while 3,4-methylenedioxymethamphetamine (MDMA), an indirect serotonin agonist, increases

PPI in healthy subjects (Liechti et al., 2001; Vollenweider, Remensberger, Hell, & Geyer, 1999). In summary there is increasing evidence that mixed D_2 / 5-HT_2 receptor antagonists modulates PPI in a way to meliorate PPI in subjects with low baseline gating while only D_2 receptor antagonists are without an effect on, or tend to attenuate, PPI in healthy volunteers. Consequently, we assume that the observed enhancing effect of sertindole on %PPI in healthy subjects exhibiting low baseline sensorimotor gating appears due to the combined impact on serotonergic and dopaminergic neurotransmission. This hypothesis supports descriptive assumptions associating normal gating functions with optimal levels of monoaminergic neurotransmission and synergistic interactions between serotonergic and dopaminergic systems (Mann et al., 2008). Moreover, it has been shown that PPI in healthy volunteers is influenced by genetic variation. For example, polimorphisms in the $5HT_{2A}R$ and COMP gene contribute to the discrimination between low and high sensorimotor gaters (Quednow et al., 2009). Therefore, future studies with large sample sizes investigating the influence of polygenetic factors on PPI and P50 suppression are warranted.

5.2.2. Sertindole increases sensory gating in healthy volunteers with low baseline P50 suppression

Until now, studies investigating the effect of antipsychotic medication on P50 suppression in healthy volunteers are scant. The majority of studies investigating schizophrenia patients treated with atypical compared to typical antipsychotics showed improved P50 suppression (Adler et al., 2004; Becker et al., 2004; Light, Geyer, Clementz, Cadenhead, & Braff, 2000) compared to non improvement (Hong et al., 2009). Only a few studies investigated the effect of antipsychotics, antidepressants or other drug compounds on P50 suppression in healthy volunteers. Therefore, a combination of haloperidol and ketamine conduct to a decrement of P50 suppression whereas the application of ketamine did not affect P50 suppression (Oranje, Gispen-De Wied, Verbaten, & Kahn, 2002). Our research group recently showed that haloperidol increases P50 suppression in subjects exhibiting low P50 gating while it disrupts P50 suppression in subjects with high P50 gating (Csomor et al., 2008a). More results about a monoaminergic influence on P50 suppression is coming from other studies. Amphetamine, an indirect monoaminergic agonist, disrupts P50 suppression (Light et al., 1999). In contrast to these findings, L-dopa, a precursor of dopamine, as well as bromocriptine, a D_2 agonist, did reduce S_1 and S_2 amplitude, but therefore, did not affect P50 suppression (Oranje et al., 2004).

Furthermore, the involvement of several other neurotransmitters in the modulation of P50 suppression is indicated by multiple studies with healthy volunteers. Therefore, N,N-dimethyltryptamine conducted to a dose-dependent attenuation of P50 suppression (Riba et al., 2002). Moreover, imipramine, significantly decreased P50 suppression (Hammer et al., 2007), whereas increased serotonergic activity evoked by the administration of a single dose of the SSRI escitalopram did not affect P50 suppression (Jensen et al., 2008). Furthermore, Yohimbine, a α_2 receptor antagonist, that enhances the release of noradrenaline by a presynaptic mechanism, disrupts P50 suppression (Adler et al., 1994). Moreover, neither a selective depletion of dopamine nor a selective depletion of serotonin had an effect on P50 suppression, while a combined monoamine depletion resulted in a decrease of P50 suppression (Mann et al., 2008). In addition, theophylline, an adenosine antagonist, conducts to a reduced P50 suppression (Ghisolfi et al., 2002). Moreover, caffeine, a non-selective adenosine receptor antagonist, reduced P50 suppression (Ghisolfi et al., 2006). The deceased and partly inconsistent findings of the involvement of different neurotransmitter in the regulation of P50 suppression in healthy volunteers might appear due to different reactions on pharmacological interventions according to subjects' baseline levels. All of the above cited studies expect the one from Csomor et al. (2008a) did not build groups of high and low baseline P50 suppression subjects. Potential pharmacological effects on P50 suppression might be hidden by the mean of all subjects and one might expect different results by stratifying subjects into low and high gaters. Beyond that, and similar as discussed for PPI, there is connotatively confirmation that atypical antipsychotics may have a restorable effect on sensory gating in schizophrenic patients, as shown for clozapine (Becker et al., 2004; Light et al., 2000; Nagamoto et al., 1996), olanzapine (Light et al., 2000) and risperidone (Light et al., 2000; Yee, Nuechterlein, Morris, & White, 1998). In summary, these results suggest that a dysfunction in several, serotonin and dopamine, as well as adenosine neurotransmitter systems might be partly responsible for the observed P50 suppression deficits in schizophrenic patients. Moreover, sertindole might also lead to a higher P50 suppression in patients suffering from schizophrenia, but this speculation has to be supported by a study investigating the effect of sertindole in schizophrenic patients.

5.2.3. The effect of sertindole on cognition in healthy volunteers

It is noteworthy that high and low PPI subjects performed differentially in a test of spatial working memory as indexed by the SWM strategy score. Subjects exhibiting high PPI chose a better strategy in solving the problem while performances in total and between errors did not differ significantly. We recently reported that subjects with low and high PPI significantly differ in their performance in the SWM task of CANTAB (Csomor et al., 2008a). High PPI levels predicted not only superior strategy formation, furthermore, a significant negative correlation between strategy score and PPI at SOA 60 level was found (Csomor et al., 2008a). Moreover, a significant negative correlation between strategy score and PPI was found by others (Giakoumaki et al., 2006). Contrary to our previous findings (Csomor et al., 2008a), there were no group differences in SWM error scores, leading to the conclusion, that even though the high PPI group chose a superior strategy, there were no performances differences between the two groups. The absence of performance differences might be an explanation for why no correlation between strategy score and PPI was observed in the present study. Furthermore, performance in SWM relies on integrity and efficiency of specific cognitive domains, e.g. relying on prefrontal cortical functioning, and therefore supports the assumption of an involvement of this area in the modulation of PPI which is supported from animal studies (Bitsios et al., 2006; Csomor et al., 2008a; Giakoumaki et al., 2006; Swerdlow et al., 2000; Swerdlow, Geyer, & Braff, 2001; Swerdlow et al., 2008). Therefore, the assumption of a presumable role of the prefrontal cortex in the modulation of PPI is supported by the different performance of high and low baseline PPI subjects in these cognitive domains. Both human and animal investigations have considered the degree to which PPI and cognition are directly associated as deminished PPI is associated with decreased cortical task-related activation in schizophrenia (Geyer, 2006; Molina et al., 2010) and perfusion measured with single photon-emission tomography (SPECT) was significantly lower in the prefrontal and premotor regions of the schizophrenic patients (Scholes & Martin-Iverson, 2009). Moreover, Kedzior, Koch and Basar-Eroglu (2007) concluded that the relationship between PPI and cognitive performance appears to be mediated by common attentional processes active in both tasks, rather than by common underlying neurophysiological inhibitory processes. Furthermore, it can be assumed that superior ability in cognitive performance in this domain is related to more efficient early information processing. However, cognitive deficits in schizophrenia spectrum disorders, especially measured by (pre)frontal tasks and confirmed by an altered neuronal activity, is a undisputable finding (Badcock et al., 2005; Hutton et al., 1998; Manoach, 2003; Minzenberg et

al., 2009; Weickert et al., 2000) with great impact on quality of life and functional outcome (Brekke, Kay, Lee, & Green, 2005; Green, 2006).

Treatment with a therapeutic beginner dose of sertindole did not lead per se to a general reduction of cognitive performances. Contrary to the present findings, it is more common, that cognitive performance in healthy volunteers is generally diminished by typical or atypical antipsychotic medication, possibly caused by sedative side effects (McCartan et al., 2001; Csomor et al., 2008a; Vollenweider et al., 2006). Sertindole seems to have no effect on muscarinic and histaminic H_1 receptors, and compared to other atypical antipsychotics exerting relatively high occupancy at these receptor sites, sertindole is not linked with anticholinergic side effects (Didriksen, 1995; Didriksen, Kreilgaard, & Arnt, 2006; Didriksen, Skarsfeldt, & Arnt, 2007; Rodefer, Nguyen, Karlsson, & Arnt, 2008; Skarsfeldt, 1996). Therefore, it is less associated with sedation while still having a satisfactory effect on both positive and negative symptoms (Arnt & Skarsfeldt, 1998; Kasper, Hale, Azorin, & Möller, 1999; Kasper, 2008; Perquin & Steinert, 2004; Zimbroff et al., 1997). More evidence for its favorable cognitive profile is coming from studies with rodents (Didriksen, 1995; Didriksen et al., 2006; Didriksen et al., 2007; Rodefer et al., 2008; Skarsfeldt, 1996). While the superior effect of potent $5HT_2$ (and relatively weaker D_2) antagonists on cognitive function has been discussed (Meltzer & McGurk, 1999), further evidence of a better impact on cognitive functions of sertindole is coming from a study with schizophrenic patients where treatment with sertindole was compared to haloperidol (Gallhofer et al., 2007). Moreover, due to the results of studies with rodents one might speculate that a combination of an absence of antimuscarinic activity and coexistent 5-HT_6 antagonistic activity might represent a key feature of sertindole leading to a positive cognitive profile (Rodefer et al., 2008). In addition, more evidence for the favorable role of 5-HT_6 antagonistic action on cognitive performance has been discussed recently (Dawson, Nguyen, & Li, 2001; Hirst et al., 2006; King, Marsden, & Fone, 2008; Lacroix, Dawson, Hagan, & Heidbreder, 2004; Marcos, Chuang, Gil-Bea, & Ramirez, 2008; Meltzer, 1994; Miguel-Hidalgo, 2001; Schaffhauser et al., 2009; Singer et al., 2009; Upton, Chuang, Hunter, & Virley, 2008; Woolley, Marsden, & Fone, 2004).

Nevertheless to reported influence of sertindole on cognition, it is notable, that the used dosage of sertindole (12 mg within 48 hours) correspond to a beginner therapeutically dosage while the therapeutic window has a range up to 20 mg per day. Therefore, the question whether a higher dose of sertindole impairs cognitive performance in healthy subject or not remains opened.

5.3. Conclusion

While, sensory gating has been proposed to be an endophenotypic biomarker for schizophrenia spectrum disorders, our studies showed that deficient sensory gating is not exclusively attributable to schizophrenia spectrum disorders. Deficient P50 gating, neither related to specific psychopathological symptoms nor to specific impairment of cognitive performance, is a robust finding in patients suffering from PTSD and adult ADHD patients. Consequently, P50 gating is not exclusively associated with a specific disorder. Furthermore, impaired P50 suppression might be a general and common feature of several psychiatric disorders sharing deficits in attention functions. However, the absence of diminished PPI in PTSD patients and adult ADHD patients seems to be a robust finding. Moreover, the influence of antipsychotics on sensory and sensorimotor gating in healthy volunteers seems to be dependent on baseline gating levels. Therefore, mixed D_2 / 5-HT_2 receptor antagonists modulate PPI as well as P50 suppression in a way to enhance it in healthy subjects with low baseline gating in a way comparable as seen in studies with schizophrenia patients. Thus, sensorimotor and sensory gating measures can be used as informative and independent neurophysiological markers for studies investigating neuropsychiatric disorders and may well constitute separable endophenotypes. While the combined use of PPI and P50 suppression in a single study might represent excellent tools for translational research, it still remains fundamental to assess established parameters for patients' studies as well as studies with healthy volunteers comparable to those coming from schizophrenia research to achieve constant and comparable and study overlapping data. While most of the studies are conducted by a crossover design, additional investigations are necessary, above all double-blind randomized longitudinal studies measuring patients before and while treated with specific medication, to investigate long lasting influences of medication on sensory gating and sensorimotor gating, and to further evaluate whether these operational measures have the potential to serve as efficacy markers for therapeutic outcome. Moreover, studies with large sample sizes investigating the influence of polygenetic factors on PPI and P50 suppression are warranted.

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CURRICULUM VITAE

Dominique H. Holstein was born 1976 in Zurich. After 10 years of school he founded a magazine for table games, role-playing games, and science fiction models. From 1998 to 2001 he concluded his neuter school-leaving examination at the “Kantonale Maturitätsschule für Erwachsene” in Zurich he studied from 2001 to 2007 psychology (main focus on neuropsychology), psychopathology and criminology at the University of Zurich. From 2007 to 2011 he concluded his Ph.D. at the department of experimental psychopathology and neuroimagine at the psychiatric university hospital of Zurich. Moreover, he started 2009 with a post gradual study for the degree of psychological psychotherapist at the Klaus Grawe Institut in Zurich. Acutally he is working as a clinical psychologist at the psychiatric clinic Sanatorium Kilchberg.